Economic evaluations of non-traditional vaccinations in middle-income countries

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Economic evaluations of non-traditional vaccinations in middle-income countries: Indonesia as a reference case

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Indonesia as a reference case

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CHAPTER 1

GENERAL INTRODUCTION

Partially adapted from:
"Expanding access to non-traditional vaccines:
a perspective from Indonesia"

Auliya A. Suwantika
Maarten J. Postma

Submitted to Expert Review of Vaccines

Introduction

Vaccinations against vaccine-preventable diseases (VPD) have been the most important contributors to reduce childhood mortality and increase life expectancy in Indonesia. Recently, the Indonesian government has launched the pentavalent vaccine (diphtheria-tetanus-pertussis (DTP), Haemophilus influenza type b (Hib) and hepatitis B) in the form of a single shot for newborn infants to reduce the mortality rate of children under five and increase the coverage of the national immunization program [1]. A 25% reduction in the mortality rate of children under five was linked to high vaccination coverage of 90% for both traditional and non-traditional vaccinations by the World Health Organization (WHO) [2]. In addition to the use of traditional vaccines (*e.g.*, tuberculosis (BCG), DTP, polio, measles and hepatitis B vaccines) in the Expanded Program on Immunization (EPI), the Indonesian government still needs to introduce additional vaccines to further reduce rates of childhood mortality. However, it typically takes at least two decades for additional vaccines to be introduced into the EPI. Several critical factors are responsible for this long delay, such as insufficient political commitment, cost of new vaccines and insufficient vaccine supply [3]. Accelerating access to non-traditional vaccines in Indonesia appears to be crucial since it will not only save the lives of children but also reduce the tremendous economic and health burdens caused by VPD. The key strategy to shorten the process of new vaccine introduction is through engaging the national decision makers on issues of primary healthcare services and convincing them with evidence on the burden of diseases for society and the potential impacts of new vaccine introductions [3].

With an annual birth cohort of approximately 4.7 million [4], Indonesia is the third biggest market in Asia, after China and India, for vaccine manufacturers. From a business perspective, the market entry hurdles for the vaccine business in Indonesia differ significantly from other pharmaceutical industries since there are two major market hurdles in the vaccine industry: (i) the high-capital investments needed to build vaccine manufacturing plants and (ii) long-term commitment of vaccine buyers [5]. Nevertheless, both hurdles become surmountable when the government commits to long-term strategic investments in vaccines. Unlike the majority of countries in the South East Asia Region (SEAR), Indonesia produces traditional vaccines domestically through Biofarma. It was the first vaccine manufacturer in the SEAR to achieve World Health Organization (WHO) prequalification status, which enabled participation in the United Nations Children's Fund (UNICEF) vaccine tenders (*e.g.*, DTP, hepatitis B, DTP-hepatitis B, measles and oral polio vaccines) [5]. With respect to non-traditional vaccines, Biofarma has been a driving force in the further development of these vaccines. For instance, in collaboration with the Murdoch

Children Research Institute (MCRI), Biofarma has been working on the development of RV3®: a new rotavirus vaccine, which is being designed to be given orally to babies at birth to provide the earliest possible protection [6]. Despite the fact that manufacturing non-traditional vaccines in mass production has the potential for application at a global scale, because of more affordable costs and higher assurance of quality, there are still two major challenges that must be overcome in Indonesia: (i) the lack of interest, incentive and support from the government for research and development, and (ii) the lack of coordination and cooperation among stakeholders, universities, research institutes, manufacturers, national regulatory authorities and the national immunization programs [2].

Once a vaccine is developed, extra challenges exist regarding the potentially high budget needed for self-sustaining storage and delivery systems for the vaccine in Indonesia because it is an archipelago country. In some cases, the introduction of non-traditional vaccines will require additional budgeting for cold chain and logistic systems. Specifically, the introduction of rotavirus vaccines obviously may require additional costs to expand cold chain capacity because the present packing volume of rotavirus vaccines is approximately 7-18 times greater than the packing volume of traditional vaccines (*e.g.*, DTP vaccines) [7]. To address this, Biofarma should consider their rotavirus vaccines' packaging and have initiatives to minimize the packing volume. With respect to the Indonesian government, they should prepare additional infrastructures and more effective vaccine management policies before they introduce a new vaccine as required by the GAVI Alliance (formerly known as the Global Alliance for Vaccines and Immunization). In particular, the WHO and UNICEF also have developed a new communication framework for new vaccine introduction, which would be included in pre-introduction phase assessments, focusing on new delivery technologies, readiness of cold chain storage, improvement of adapted vaccines and training of health care workers. These requirements were primarily designed to assure a country's systematic readiness when introducing new interventions and more specifically, to minimize failure due to economic factors.

During the period from 2006-2011, Indonesia's Gross Domestic Product (GDP) per capita grew from US$ 1,601 to US$ 3,472 [8], allowing Indonesia to graduate from the level of lower-income country (LIC) to middle-income country (MIC). Even though its GDP per capita had increased significantly, the Indonesian government expenditure on the EPI fluctuated over this period. In 2011, the Indonesian government spent US$ 68 million on the EPI (US$ 14 per infant) for seven traditional immunizations [9]. In addition to supporting the EPI, the Indonesian government also spent US$ 61 million on vaccines during the same period [9]. Given these limited budgets, the implementation of non-traditional vaccines in Indonesia

appears to be dependent on the financing arrangement surrounding the immunization programs. However, decisions related to these financing matters are usually complicated, even in a high-income country (HIC) [10]. The selection among financing options should be made while estimating the number of required resources to achieve the EPI's goals, such as access, utilization, quality, safety and equity [10]. The financing arrangement also should be chosen with an understanding of the specific characteristics of each option.

In order to enhance the practical market for vaccines and the introduction of non-traditional vaccines, future approaches should address several priorities: (i) greater access and equity with respect to the coverage of the EPI, (ii) well-implemented, accelerated disease control and prevention strategies, and (iii) development of a public-health infrastructure. It should be noted that introduction of new interventions against infectious diseases, including the use of new vaccines, is often strongly associated with less frequent use of hospital services and lower hospital costs. Therefore, accelerating the introduction of non-traditional vaccines appears to be in line with the policy of several preventative efforts, such as lowering antibiotic use, reducing antimicrobial resistance, and extending herd immunity and protection effects. Another important benefit to the health system facilitated by new vaccine introduction is the increase in awareness of improving disease surveillance.

In conclusion, since access to endemic and non-traditional vaccines is still needed in Indonesia, further economic evaluation studies of adding non-traditional vaccines to the routine immunization schedules are required. Decisions to introduce additional vaccines must be supported with clear strategies to guarantee the supply of affordable vaccines and financial sustainability.

Aim and outline of the thesis

The general aim of this thesis is to propose a framework on economic evaluations of non-traditional vaccinations in Indonesia, as a MIC with limited immunization budget, by using two reference cases of rotavirus and hepatitis A vaccines in the first and second part of this thesis, respectively. In the first part of this thesis, the cost-effectiveness of rotavirus immunization in Indonesia is explored initially by taking breastfeeding patterns into account (Chapter 2). A further research that considers the effect of breastfeeding promotion interventions is presented in Chapter 3. To give an idea of the situation in another MIC, we analyze the cost-effectiveness of rotavirus immunization in Hangzhou, China by making a comparison between two vaccines (Chapter 4). Based on the summary of evidence supporting introduction of rotavirus vaccination in Indonesia, in Chapter 5, we discuss the constraints and draw upon experiences from other countries to propose strategies on

accelerating the introduction of rotavirus immunization in Indonesia. While in the second part of this thesis, a comprehensive picture of hepatitis A vaccination in MICs is presented in a systematic review (Chapter 6). In particular, a cost-effectiveness analysis of hepatitis A vaccination in Indonesia is discussed specifically in Chapter 7. At last, the main findings of the studies as presented in the previous chapters are summarized and discussed in Chapter 8 by providing several policy recommendations for policy makers in Indonesia to expand sustainable immunization programs in the future.

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CHAPTER 2

Cost-effectiveness of rotavirus immunization in Indonesia: taking breastfeeding patterns into account

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Abstract

Objective

This study aims to assess the cost-effectiveness of rotavirus immunization in Indonesia, taking breastfeeding patterns explicitly into account.

Method

An age-structured cohort model was developed for the 2011 Indonesia birth cohort. Next, we compared two strategies, the current situation without rotavirus immunization versus the alternative of a national immunization program. We applied a 5-year time horizon, with 1 monthly analytical cycles for children less than 1 year of age and annually thereafter. Three scenarios were compared to the base-case reflecting the actual distribution over the different breastfeeding modes as present in Indonesia: *i.e.,* the population under 2 years old with (i) 100% exclusive breastfeeding, (ii) 100% partial breastfeeding and (iii) 100% no breastfeeding. Monte Carlo simulations were used to examine the economic acceptability and affordability of the rotavirus vaccination.

Results

Rotavirus immunization would effectively reduce severe cases of rotavirus during the first 5 years of a child's life. Under the market vaccine price the total yearly vaccine cost would amount to US$ 65 million. The incremental cost per quality-adjusted-life-year (QALY) in the base-case was US$ 174 from the societal perspective. Obviously, it was much lower than the 2011 Indonesian Gross Domestic Product (GDP) per capita of US$ 3,469. Affordability results showed that at the GAVI-subsidized vaccine price, rotavirus vaccination could be affordable for the Indonesian health system. Increased uptake of breastfeeding might slightly reduce cost-effectiveness results.

Conclusion

Rotavirus immunization in Indonesia would be a highly cost-effective health intervention even under the market vaccine price. The results illustrate that rotavirus immunization would greatly reduce the burden of disease due to rotavirus infection. Even within increased uptake of breastfeeding, cost-effectiveness remains favorable.

Introduction

Despite the growing number of diarrheal disease in Indonesia, the burden of rotavirus diarrhea as the major cause of diarrheal disease is poorly documented [1,2]. Indonesia was one of the countries in Asia, which received support from PATH's Rotavirus Vaccine Program to strengthen the World Health Organization's (WHO)'s expanded immunization recommendations on promoting the global use of rotavirus vaccines [3]. Since 2001, according to the WHO's generic protocol, a longitudinal survey of rotavirus infection through the Indonesian Rotavirus Surveillance Network (IRSN) has been conducted in six hospitals in Indonesia [1]. The prospective surveillance in 2006 showed that rotavirus infections were responsible for the majority of severe diarrhea in children under 5 years old occurring throughout the year mainly in children aged between 6-24 months old [1].

Breastfeeding is considered to protect against rotavirus infections [4]. The main component of breast milk that is thought to protect against rotavirus infection is lactadherine [4-6]. The WHO estimated that breastfeeding in accordance with the WHO's recommendations would save 1.45 million children's lives each year in developing countries due to diarrhea disorders and lower respiratory tract infections [5]. The United Nations Children's Fund (UNICEF) and the WHO issued a recommendation that children should be breastfed for at least six months to reduce the morbidity and mortality rate [7]. In 2003, the Indonesian government changed the recommended duration of exclusive breastfeeding from four to six months.

The Indonesian government needs to assess the economic benefits and health outcomes of such a vaccination program before routine rotavirus immunization can be recommended [8]. In terms of economic and financial perspectives, implementation of rotavirus vaccine should ideally be cost-effective. However, it would be difficult to implement rotavirus immunization in the National Immunization Program (NIP) if the vaccine price is not affordable. Determining the financial resources needed is important to estimate the entire cost or budget impact of the vaccination program, even at the prevailing market price [9].

Up to now, only one economic evaluation study on rotavirus immunization has been conducted in Indonesia [8], suggesting that implementation of rotavirus immunization in National Immunization Program (NIP) would be a cost-effective intervention in Indonesia. However, it only evaluated the use of the 2-dose vaccine while ignoring the potential impacts of the 3-dose vaccine in the NIP. Additionally, the previous study applied the vaccine efficacy in a condition of without breastfeeding and it did not take breastfeeding patterns explicitly into account. Notably, further increasing breastfeeding would be in line with the WHO's recommendations on that matter. However, this might impact the economic evaluation

results for rotavirus vaccination as maternal protection would be enhanced leaving less room for the preventive effect of the vaccine. Hence, it is important to know whether potential favorable cost-effectiveness remains within the context of the Indonesian policy to enhance the uptake of breastfeeding. The objective of this study is to assess the cost-effectiveness of rotavirus immunization in Indonesia, taking breastfeeding patterns explicitly into account.

Methods

Model

Considering the limitations of previous study and motivated by exploring the impact of breastfeeding in childhood vaccination, we performed a cost-effectiveness analysis on rotavirus immunization focusing on the use of Rotateq® as one of the recommended 3-dose rotavirus vaccines. Differing from previous studies on similar topic and model [8,10-13], we explicitly took breastfeeding patterns into account and compared three scenarios to the base-case reflecting the actual distribution over the different breastfeeding modes as present in Indonesia: *i.e.,* the population under 2 years old with (i) 100% exclusive breastfeeding (EBF), (ii) 100% partial breastfeeding (PBF) and (iii) 100% no breastfeeding (NBF). The vaccination program was compared to the condition without vaccination in the situations of the actual breastfeeding pattern (base-case) and specific scenarios.

In this study we applied an age-structured cohort model based on a decision tree model, developed by University of Groningen labeled "Consensus Model on Rotavirus Vaccination" (CoRoVa), which has been used previously for both developing and developed countries [10,11], to assess the cost-effectiveness and affordability of implementing universal rotavirus immunization based on the GAVI-subsidized vaccine price and market vaccine price, in the context of the Indonesian healthcare system for the next 5 years (see Fig. 1). We applied this model because of its ability to account all relevant epidemiological parameters, economic aspects and characteristics of the vaccine, inclusive potential waning immunity [14], and it was also readily available to us. In particular, we used a birth cohort of 4,200,000 infants [8] in this age-structured cohort model and applied a 5-year time horizon with 1 month analytical cycles for children less than 1 year of age and annual cycles beyond 1 year.

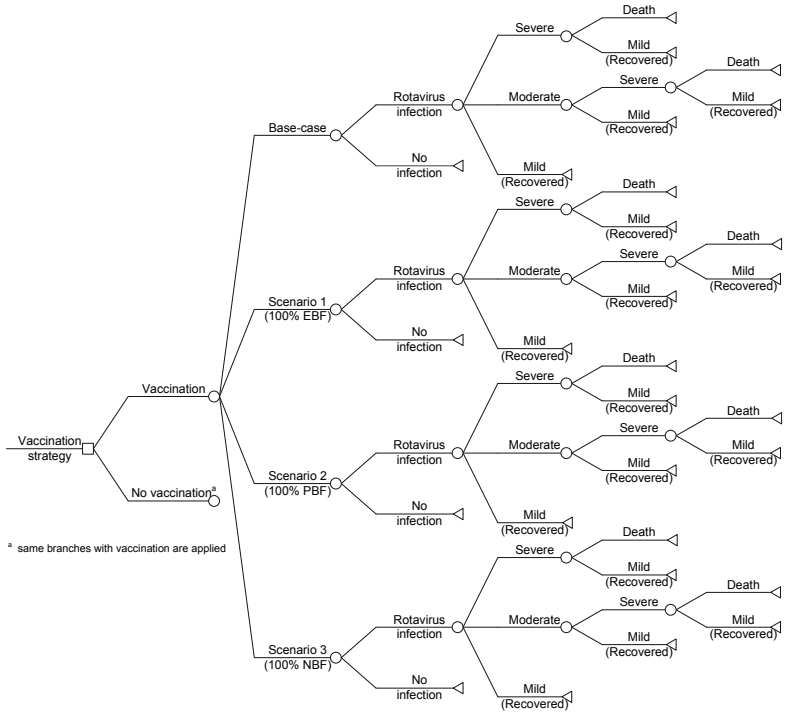

Fig. 1. Decision analytic model for estimating the cost-effectiveness of rotavirus immunization in Indonesia

Disease burden estimates

Using the data from the Indonesian Demographic and Health Survey (IDHS) 2007 on age patterns of breastfeeding, we populated under-5-year-old population based on breastfeeding statuses as the actual distribution over the different breastfeeding modes as present in Indonesia: 3.8% EBF, 59.8% NBF and 36.4% PBF [15]. Health outcomes from this model were classified by the four levels of rotavirus-diarrhea severity that are generally used: mild, moderate, severe and death [2]. We assumed that mild disease requires home treatment, moderate requires general practitioner (GP) treatment and outpatient visits, while severe cases were assumed to require hospitalization [10,11]. This classification is in line with a study, which was done previously for global assessments [2]. The model was programmed in Microsoft Excel 2010 and @Risk 4.5.4. was used for probabilistic sensitivity analysis.

We estimated rotavirus-diarrhea cases from diarrhea cases in Indonesia. Firstly, we classified the Indonesian 2011 population under 5 years old based on breastfeeding status using data from IDHS 2007 on breastfeeding status by age (0-3 years), extrapolated to the whole under-5-year-old population. We divided the population into the relevant age groups: 0-6, 6-11, 12-23, 24-35, 36-47 and 48-59 months [15]. In the compared scenarios, we

assumed that the proportions of breastfeeding population under 2 years old are 100% EBF, 100% PBF and 100% NBF for scenario 1, 2 and 3, respectively. We considered a time horizon of 2 years in our breastfeeding scenario as WHO recommended exclusive breastfeeding for the first six months of life and supplemented breastfeeding continued up to two years or beyond [7]. For 36-47 months, we assumed that the proportions over breastfeeding status are 90% NBF, 10% PBF, 0% EBF, whereas for 48-59 months we assumed 100% NBF. Related to the diarrhea cases in under-5-year-old children, we used 2007 data from a previous study in Indonesia as a base-case [8]. We assumed the same number of diarrhea cases for 2011 as analyzed for 2007. For the scenarios compared, we estimated diarrhea cases explicitly based on breastfeeding distribution. Considering the relative risk of diarrhea from IDHS 2007 and the WHO's algorithm for calculating relative risk of diarrhea morbidity by feeding mode [16], we estimated 2011 diarrhea cases for under-5-year-old children depending on breastfeeding status for base-case and all scenarios. Secondly, we applied the same approach to calculate 2011 rotavirus-diarrhea cases for under-5-year-old children in base-case and all scenarios by considering the percentage of patients with rotavirus-diarrhea from the number of patients with diarrhea enrolled in each age group from previous study about burden of rotavirus-diarrhea in Indonesia [1]. Finally, we classified rotavirus-diarrhea cases into the four levels of severity by applying proportions of 1.1% for death, 22.9% for hospitalization (severe cases) and 76.0% for outpatient visit (moderate and mild cases) on rotavirus-diarrhea cases [8]. Furthermore, we estimated that moderate would make up 38.7% and mild 61.3% from outpatient visit cases, based on a previously published application of CoRoVa to the South East Asia Region (SEAR) [14]. Notably, we obtained the number of rotavirus-diarrhea cases in four levels of severity adjusted by age for base-case and all scenarios, consistently considering the same age groups in our adjustments (see Fig. 2).

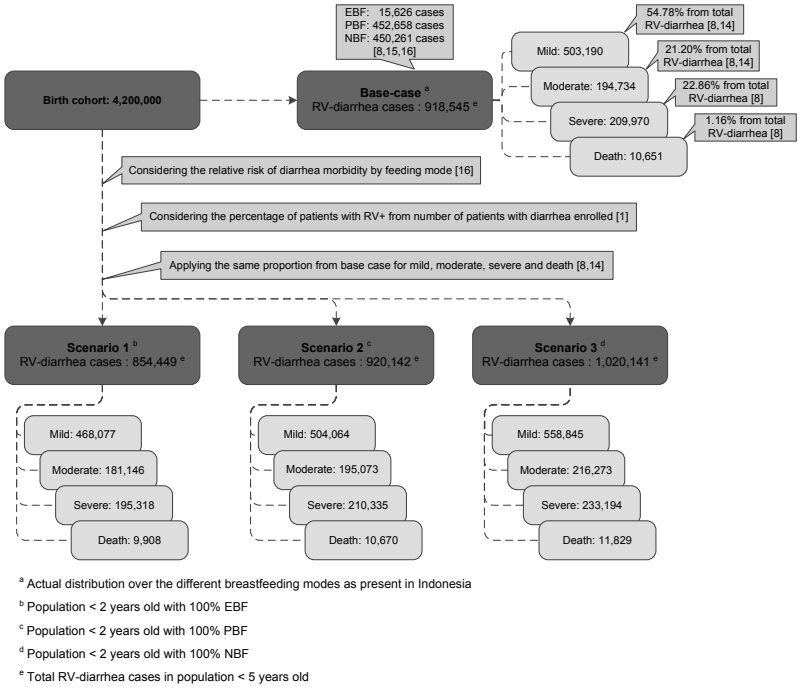

Fig. 2. Scheme for estimation of rotavirus-diarrhea cases in Indonesia

Vaccine efficacy, waning immunity and between-dose efficacy

Rotavirus vaccine efficacy was estimated to be 84% for the prevention of rotavirus-associated hospitalizations, 70% for the prevention of outpatient visits and 76.5% for prevention of deaths [8]. We assumed these percentages as initial effectiveness of the vaccine for the outcomes: severe, mild/moderate and death, respectively. We applied the vaccine effectiveness from a previous study in Indonesia without breastfeeding [8]. We corrected this vaccine effectiveness in our model taking the estimated effect of breastfeeding patterns into account by considering the WHO's algorithm for calculating relative risks of diarrhea morbidity by feeding mode for all scenarios [16]. We conservatively assumed that vaccine efficacy would exponentially decrease by 11% per year starting after the first year (waning) based on a previous study [11].

To estimate in-between dose efficacy for a 3-dose Rotateq® vaccine, we applied data from a previously published study where the between-dose efficacy is 82% for first and second doses and 84% for second and third doses [11,17,18]. Based on those data, we estimated vaccine effectiveness against fatal cases between first and second doses at 62.7% (0.82 x 76.5%) and between second and third doses at 64.3% (0.84 x 76.5%) [11,17,18]. We applied

the same rates of 0.82 and 0.84 to estimate between-dose efficacies for mild, moderate and severe cases [11]. For vaccine coverage, we assumed that Rotateq® vaccine would be administered at the same time with the DPT vaccine in Indonesia based on data from WHO and UNICEF. The 2011 DPT vaccine coverage of 94% would also be applicable for vaccination with Rotateq® [19] (see Table 1).

Outcome measures

In absence of available data on quality-adjusted-life-year (QALY) losses in Indonesia due to rotavirus infection, we estimated the QALY losses in affected infants and children by considering the duration of illness at 4, 8, 11 and 365 days for mild, moderate, severe and fatal cases, respectively, and applying a number of earlier works in SEAR [10,11,14], which were discounted at a 3% rate (see Table 1).

Costs

The analysis was done from both the healthcare perspective (only direct medical costs) and the societal perspective (direct medical, direct non-medical and indirect costs). Direct costs (medication, diagnostics and bed cost), direct non-medical (transportation) and indirect costs (productivity loss due to rotavirus-diarrhea by the caregiver) due to rotavirus-related severe and moderate cases were estimated from hospitalization data and outpatient visit costs from a cost study previously conducted in Indonesia [8]. For mild cases, we estimated direct medical cost from the expenditure per child of oral-rehydration-therapy (ORT) in diarrhea treatment for children less than 5 years of age [20], while for direct non-medical and indirect costs, we applied the same number with moderate cases [8]. We did not include mortality costs in this study to avoid double counting [21]. All cost items were available in 2007 prices and we converted them to 2011 US$ using the underlying growth rate in consumer prices. Based on a 2011 study in Vietnam, the prices of Rotateq® were assumed at US$ 5 per dose and US$ 0.3 per dose for the market price and the GAVI-subsidized price, respectively. We applied these in Indonesia with 2011 setting. We assumed the price in 2011 will be the same for Vietnam and Indonesia. We applied the cost of vaccine administration at US$ 0.5 based on a 2009 study in Indonesia [8]. Obviously, all costs were discounted with a yearly rate of 3% (see Table 1).

ICER analysis

The incremental cost-effectiveness ratio (ICER) was analyzed in the base-case and three other scenarios. We additionally calculated the impacts of market price on each ICER values.

We evaluated the results of rotavirus vaccination in Indonesia by using the WHO's definition on cost-effectiveness of universal immunization according to the GDP per capita, (i) highly cost-effective (less than one GDP per capita); (ii) cost-effective (between 1 and 3 times GDP per capita); and (iii) cost-ineffective (more than 3 times GDP per capita) [22].

Sensitivity and budget impact analyses

We performed several sensitivity analyses in this study including univariate sensitivity and probabilistic analyses [11]. Univariate sensitivity analyses were performed to investigate the effects of different input parameters on cost and health outcomes, by varying each parameter at value of ± 25 % while keeping other parameters constant. Regarding the breastfeeding patterns, we varied from 100% NBF as the worst condition of breastfeeding to 100% EBF as the best condition of breastfeeding in several scenarios. Probabilistic sensitivity analysis (PSA) was provided by running 5,000 Monte Carlo simulations using @Risk 4.5.4. Distributions associated with input parameters are shown in Table 1. The PSA results are presented in cost-effectiveness acceptability curves (CEACs) from a societal perspective for all scenarios by using two thresholds, ICER at the base-case value and GDP per capita.

Based on the distribution of incremental costs and health gains from 5,000 simulations, we evaluated affordability in base-case related to the required budget for vaccination (vaccination costs + treatment costs) from the healthcare perspective to describe the budget impacts on the implementation of rotavirus vaccination.

Table 1
Parameters used in the economic model

Parameters	Base-case value	Distribution	References
Vaccine coverage	94%	Triangular (89%; 94%; 99%)	[19]
Vaccine efficacy			
Mild	70%	Triangular (67%; 70%; 74%)	[8]
Moderate	70%	Triangular (67%; 70%; 74%)	
Severe	84%	Triangular (80%; 84%; 88%)	
Death	76.5%	Triangular (73%; 76.5%; 80%)	
Incidence rates of rotavirus-diarrhea			
No breastfeeding			
Mild	0.01134	Normal (90%CI; 0.01129-0.01138)	[8, 11, 14];
Moderate	0.00439	Normal (90%CI; 0.00436-0.00441)	calculated
Severe	0.00473	Normal (90%CI; 0.00470-0.00476)	
Death	0.00024	Normal (90%CI; 0.00023-0.00025)	
Exclusive breastfeeding			
Mild	0.00039	Normal (90%CI; 0.00039-0.00040)	[8, 11, 14];
Moderate	0.00015	Normal (90%CI; 0.00015-0.00016)	calculated
Severe	0.00016	Normal (90%CI; 0.00016-0.00017)	
Death	0.00001	Normal (90%CI; 0.000007-0.00001)	
Partial breastfeeding			
Mild	0.01140	Normal (90%CI; 0.01135-0.01144)	[8, 11, 14];
Moderate	0.00441	Normal (90%CI; 0.00438-0.00444)	calculated
Severe	0.00476	Normal (90%CI; 0.00473-0.00478)	
Death	0.00024	Normal (90%CI; 0.00023-0.00025)	
Utility losses			
Mild	0.00164	Triangular	[10, 11, 14]
Moderate	0.00548	(using 25% lower and upper)	
Severe	0.02110		
Death	1.00000		
Total medical direct costs per case (healthcare perspective, US$)			
Mild	1.44	Triangular (1.08; 1.44; 1.80)	[20]
Moderate	4.31	Triangular (3.23; 4.31; 5.39)	[8]
Severe	41.72	Triangular (31.29; 41.72; 52.15)	[8]
Total direct and indirect costs per case (societal perspective, US$)			
Mild	2.81	Triangular (2.11; 2.81; 3.52)	[20]
Moderate	5.69	Triangular (4.27; 5.69; 7.11)	[8]
Severe	56.34	Triangular (42.25; 56.34; 70.42)	[8]
Total vaccination and administration cost (per child, US$)			
3-dose, Market price	15.50	Alternative scenario	[8,11]
Discount rate	3%	Unvaried	[8]

Results

Rotavirus cases and cost of illness

In the situation representing the actual combination over the different breastfeeding modes as present in Indonesia currently (base-case) and assuming 94% vaccine coverage [19], vaccination of 4,200,000 birth cohort [8] would reduce rotavirus-diarrhea by 237,368 mild cases, 91,861 moderate cases, 117,110 severe cases and 5,450 deaths. Furthermore, it would save 304,433 discounted QALYs and costs due to rotavirus-diarrhea at US$ 5,111,919 and US$ 7,033,814 from the healthcare and societal perspective, respectively. Comparing other scenarios with the base-case, rotavirus vaccination would obviously give the highest reduction of rotavirus cases, QALYs lost and cost-of-illness averted if no uptake of breastfeeding would exist (scenario 3) (see Table 2).

Table 2
Results from all scenarios

	No Vaccination	Vaccination [i]	Difference
Base-case [a]			
Number of RV-diarrhea cases [e]	918,545	466,756	451,789
Mild cases	503,190	265,822	237,368
Moderate cases	194,734	102,873	91,861
Severe cases	209,970	92,860	117,110
Death cases	10,651	5,201	5,450
QALYs lost [f]	617,356	312,923	304,433
Cost of illness (healthcare perspective) [f,g]	$ 9,718,341	$ 4,606,422	$ 5,111,919
Cost of illness (societal perspective) [f,h]	$ 13,415,029	$ 6,381,216	$ 7,033,814
Scenario 1 [b]			
Number of RV-diarrhea cases [e]	854,449	444,551	409,898
Mild cases	468,077	252,632	215,446
Moderate cases	181,146	97,768	83,377
Severe cases	195,318	89,186	106,132
Death cases	9,908	4,965	4,943
QALYs lost [f]	571,519	298,368	273,150
Cost of illness (healthcare perspective) [f,g]	$ 9,011,051	$ 4,413,572	$ 4,597,479
Cost of illness (societal perspective) [f,h]	$ 12,438,698	$ 6,112,735	$ 6,325,963
Scenario 2 [c]			
Number of RV-diarrhea cases [e]	920,141	476,352	452,789
Mild cases	504,064	266,173	237,891
Moderate cases	195,073	103,009	92,064
Severe cases	210,335	92,963	117,372
Death cases	10,670	5,208	5,462
QALYs lost [f]	618,496	313,315	305,182
Cost of illness (healthcare perspective) [f,g]	$ 9,736,138	$ 4,610,521	$ 5,125,616
Cost of illness (societal perspective) [f,h]	$ 13,439,596	$ 6,386,935	$ 7,052,661
Scenario 3 [d]			
Number of RV-diarrhea cases [e]	1,020,141	502,108	518,033
Mild cases	558,845	286,811	272,035
Moderate cases	216,273	110,996	105,277
Severe cases	233,194	98,725	134,469
Death cases	11,829	5,577	6,252
QALYs lost [f]	690,006	336,098	353,908
Cost of illness (healthcare perspective) [f,g]	$ 10,839,814	$ 4,909,978	$ 5,929,836
Cost of illness (societal perspective) [f,h]	$ 14,963,091	$ 6,803,853	$ 8,159,238

[a] Actual distribution over the different BF patterns
[b] Population under 2 years old with 100 % EBF
[c] Population under 2 years old with 100 % PBF
[d] Population under 2 years old with 100 % NBF
[e] Population under 5 years old
[f] Discounted
[g] Direct medical cost
[h] Direct medical + direct non-medical + indirect costs
[i] Costs are excluding vaccination cost

Cost-effectiveness results

In the base-case, with a market price of US$ 5 per dose [11], ICERs from the societal perspective (US$ 174) and from the healthcare perspective (US$ 181) are far below the 2011 Indonesian GDP per capita of US$ 3,495 [23]. It strongly suggests that rotavirus immunization is a highly cost-effective intervention for the Indonesian healthcare system according to the WHO's definition for cost-effectiveness [22]. Regarding the breastfeeding modes, ICERs from scenario 3 are US$ 146 and US$ 153 from the societal perspective and the healthcare perspective, respectively, reflecting the lowest values compared to other breastfeeding modes. With an optimal breastfeeding in under-2-year-old population (scenario 1), cost-effectiveness would increase to US$ 203 and US$ 197 in both perspectives, yet the ICERs are still far under the WHO threshold (see Fig. 3).

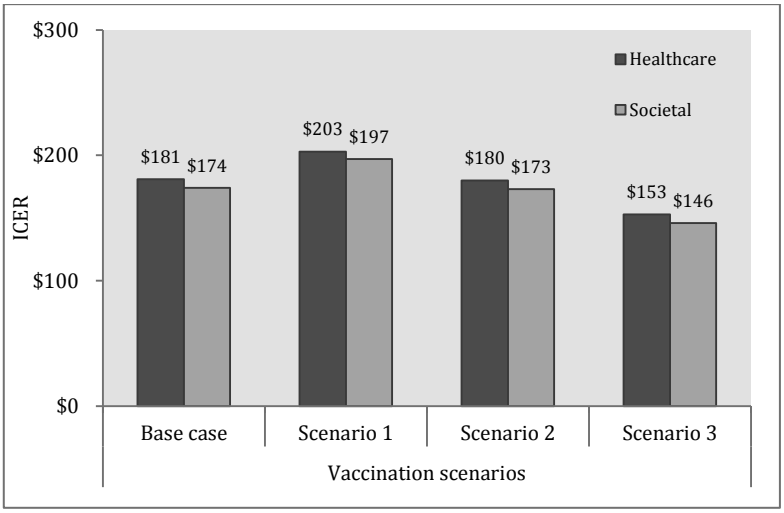

Fig. 3. Cost-effectiveness value for all scenarios

Univariate sensitivity analyses

The impacts of parameter changes on the ICERs are shown in a tornado chart (see Fig. 4). The results confirmed that the mortality rate, breastfeeding patterns, total severe cost and severe incidence were the most influential parameters in the sensitivity analyses. The cost-effectiveness results were not sensitive to the total moderate cost, moderate incidence, total mild cost and mild incidence.

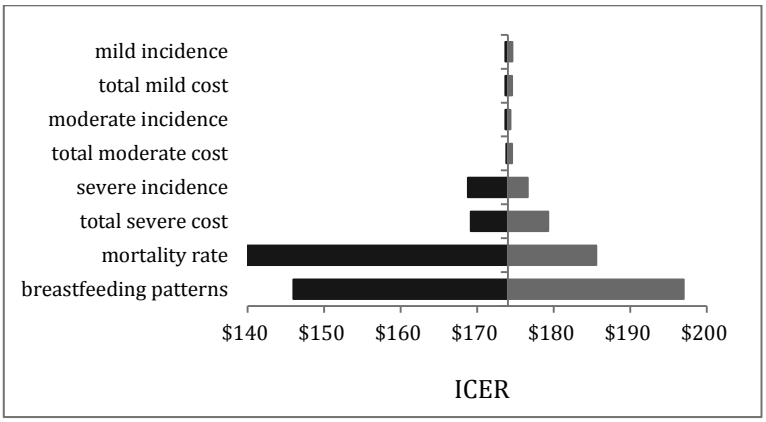

Fig. 4. Univariate sensitivity analyses

Cost-effectiveness acceptability curves (CEACs)

The CEACs showed that at the threshold ICER of US$ 174 (the base-case value from the societal perspective), the probability for the vaccination program to be cost-effective would be 47%, 0%, 59% and 100% for the base-case and scenarios 1, 2 and 3, respectively. If a US$ 3,495 (GDP per capita) threshold would be used, 100% of simulations resulted in acceptable ICERs for all scenarios and the base-case (see Fig. 5a). From the societal perspective, cost-effectiveness acceptability curves show the probability that universal newborn rotavirus immunization in Indonesia is cost-effective at different cost-effective threshold values [11].

Affordability curves

Fig. 4 shows affordability where rotavirus vaccine is purchased at the market price and when it is subsidized by the GAVI, US$ 0.3 per dose [11]. At the market price or GAVI-subsidized price, affordability curves showed that rotavirus vaccination is affordable (for the birth cohort of 4,200,000) as a function of the budget constraint, from the healthcare perspective. At the budget of US$ 10,175,000 and US$ 64,940,000 for the GAVI-subsidized price and the market price, respectively, vaccination would be 100% affordable. However, it would not be affordable when the budget does not exceed US$ 10,095,000 and US$ 64,860,000 at the GAVI-subsidized price and the market price, respectively (see Fig. 5b).

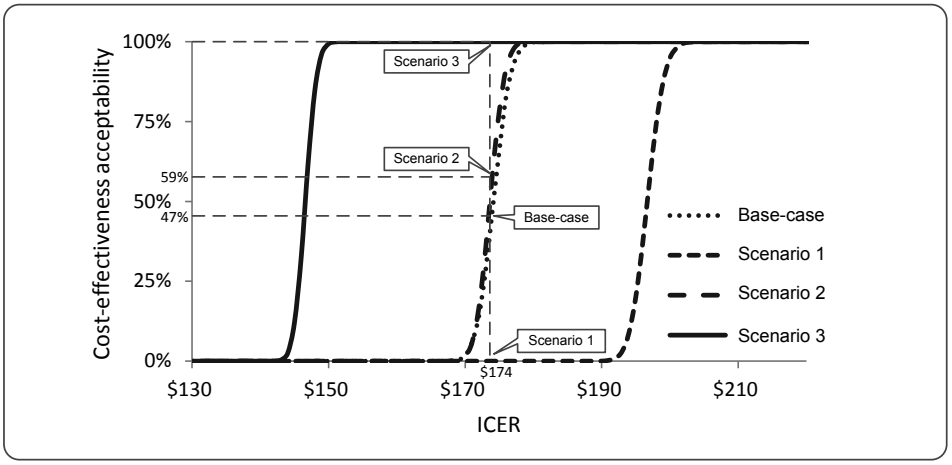

Fig. 5a. Cost-effectiveness acceptability curves from the societal perspective

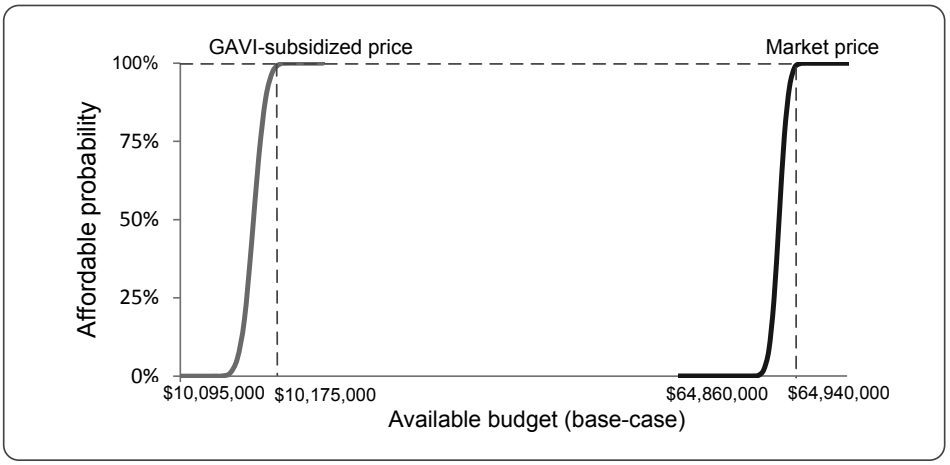

Fig. 5b. Affordability curves from the healthcare perspective (base-case)

Discussion

In the absence of vaccination, rotavirus cases under 5 years old are 918,545; 854,449; 920,141 and 1,020,142; for the base-case, scenario 1, 2 and 3, respectively. Applying vaccine efficacy at 70%; 84% and 76.5% for mild-moderate, severe and fatal cases, respectively, vaccination would decrease rotavirus-diarrhea cases under 5-years-old of 451,789; 409,898; 452,789 and 518,033, respectively. Vaccination also would decrease costs due to rotavirus from the healthcare perspective by US$ 5,111,919; US$ 4,597,479; US$ 5,125,616 and US$ 5,929,836, respectively. From the societal perspective, it would decrease costs due to rotavirus by US$ 7,033,814; US$ 6,325,963; US$ 7,052,661 and US$ 8,159,238. The cost-

effectiveness analyses yielded ICERs from the societal perspective at US$ 174, US$ 197, US$ 173 and US$ 146, respectively, for the base-case, scenario 1, 2 and 3.

Our assumption that breastfeeding protects young children against rotavirus infections is congruent with other studies [4]. Our results seem similar with a previous study in Indonesia on the same subject [8], confirming that rotavirus vaccination would be a cost-effective public health intervention for Indonesia. This further supports the WHO's recommendations on universal rotavirus immunization. The sensitivity analyses showed that the mortality rate, breastfeeding patterns, total severe cost and severe incidence were the most influential parameters impacting the cost-effectiveness results. The results on this study reconfirmed the results from previous studies on cost-effectiveness of rotavirus immunization [10,24,25]. A critical review on cost-effectiveness of rotavirus vaccination previously mentioned that the most influential parameter for middle and low income countries is the mortality rate [24]. Shim *et al.* indicated that breastfeeding would have substantial impacts in the context of exploring impact on the effectiveness of rotavirus vaccines [25]. Additionally, a previous study in the Netherlands mentioned that cost-effectiveness results were sensitive to the cost of hospitalization (severe cases) [10].

Our study provides information for policy makers on the potential introduction of rotavirus immunization into the NIP. At the current market price of US$ 5 per dose, a rotavirus immunization program in Indonesia could be a highly cost-effective intervention according to the WHO's criteria for cost-effectiveness. Furthermore, when we took uncertainties into account, affordability analysis indicated that there was a significant difference in required funds for rotavirus vaccination in Indonesia under the GAVI-subsidized and market situations. At the GAVI-subsidized price of US$ 0.3 per dose, rotavirus vaccination would not be affordable when the budget does not exceed US$ 12 million, while at the market price of US$ 5 per dose, it would not be affordable when the budget does not exceed US$ 67 million. In fact, the Indonesian government spent approximately US$ 198 million for NIP activities in 2011 [26]. Compared to the total Indonesian government health budget for the whole mandatory immunization program (hepatitis B, BCG, DTP, measles and polio), the required investment by the government for universal rotavirus vaccination in case of no GAVI support would be more than a third. It means that inclusion of rotavirus immunization would be unrealistic if the Indonesian government had to fully finance it by itself without the GAVI support. A solution could be to reduce the vaccine price through subsidy by international organizations. Leaving funds available could enhance implementation of further vaccination programs (*e.g.,* vaccination against Hepatitis A).

Notably, the Indonesian government could decide to develop a new rotavirus vaccine by itself. In particular, the Indonesian government is already considering to manufacture a rotavirus vaccine in mass production in Indonesia through Biofarma [27]. This is important for long-term sustainability of vaccine supply as potential GAVI's support for rotavirus immunization will eventually end and in the future Indonesian government should finance vaccination by itself. It is reassuring though that, even at the market price of US$ 5 per dose, rotavirus vaccination would be a highly cost-effective strategy in Indonesia and that likely the market price of rotavirus vaccine will further decline in the future due to competition among vaccine manufacturing companies.

We do not present the first economic analysis of rotavirus vaccination in Indonesia. Next to reinforcing the results of one previous study, our study does have some novelties. In particular, a generic model that was previously applied in both developed and developing countries has shown its worth in both settings. Therefore, this study could be performed while applying the WHO's recommendations guiding the model design for low income countries. Additionally, our study took breastfeeding explicitly into account. The relationship between breastfeeding and rotavirus infection is well-established and therefore important to be included in the modeling approach. We specifically compared three breastfeeding models in this study. The advantage of including breastfeeding model is the ability to confirm the impact of different breastfeeding patterns in our economic evaluation results. Finally, another difference referred to our application of an age-structured cohort model, which has abilities to capture multiple infections per infected child and waning immunity.

Nevertheless, we encountered several limitations in our study. The first limitation of our analysis is the application of a static model, instead of applying a dynamic continuous model that allows the inclusion of herd immunity effects in the analysis. The lack of detailed data hampered the use of a dynamic model in this study. However, if the herd immunity had been included in the analysis, there would be greater impacts of rotavirus vaccination and stronger favorable cost-effectiveness. Another limitation is the lack of specific rotavirus related diarrhea specific incidence data in Indonesia. As we applied 2007 data from previous study and assumed it would be the same with 2011, these assumptions were varied extensively in multiple sensitivity analysis. Finally, treatment costs were only available for 2007 and had to be adjusted to reflect in 2011 values. Obviously, rotavirus vaccination would be more cost-effective if treatment costs of the disease have increased in the meantime.

From the health-economic perspective, the Indonesian government should seriously consider the introduction of rotavirus vaccination. Concomitantly, increasing breastfeeding rate could be considered as one of WHO-supported programs. It has been shown that

rotavirus vaccination remains cost-effective with increased uptake of breastfeeding. Obviously, hurdles to be successful in implementing vaccination exist, as generally this might be difficult for a developing country as Indonesia with limited resources. Next to vaccine costs, as an archipelago country, extra challenges exist regarding a potential high budget for a self-sustaining storage and delivery system for the vaccine. However, realistic solutions could certainly be found to overcome difficulties, for example through funding from international organizations for developing countries. Hopefully, the results of this study assist policy makers in deciding an optimal and rational strategy to reduce rotavirus infection in children and attain the WHO's goal on universal rotavirus immunization.

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CHAPTER 3

Effect of breastfeeding promotion interventions on cost-effectiveness of rotavirus immunization in Indonesia

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Maarten J. Postma

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Abstract

Background

Rotavirus infection has been reported to be responsible for the majority of severe diarrhea in children under 5 years old in Indonesia. Breast milk is considered to protect against rotavirus infection and increasing breastfeeding promotion programs could be an alternative target to reduce the incidence of rotavirus diarrhea. This study aims to investigate the effect of breastfeeding promotion interventions on cost-effectiveness of rotavirus immunization in Indonesia, focusing on breastfeeding education and support interventions.

Methods

An age-structured cohort model was developed for the 2011 Indonesia birth cohort. We compared four interventions in scenarios: (i) base-case (I_0) reflecting the current situation for under-5-year-old population, (ii) with an additional breastfeeding education intervention (I_1), (iii) with a support intervention on initiation and duration (I_2) and (iv) with both of these two interventions combined (I_3). The model applied a 5-year time horizon, with 1 month analytical cycles for children less than 1 year of age and annually thereafter. Monte Carlo simulations were used to examine the economic acceptability and affordability of the rotavirus vaccination.

Rotavirus immunization would effectively reduce severe cases of rotavirus during the first 5 years of a child's life even assuming various breastfeeding promotion interventions. The total yearly vaccine cost would amount to US$ 64 million under the market vaccine price. Cost-effectiveness would increase to US$ 153 (societal perspective) with an optimal breastfeeding promotion intervention. Obviously, this is much lower than the 2011 Gross Domestic Product (GDP) per capita of US$ 3,495. Affordability results showed that at the market vaccine price, rotavirus vaccination could be affordable for the Indonesian health system

Conclusions

Rotavirus immunization would be a highly cost-effective public health intervention for Indonesia even under various breastfeeding promotion interventions based on the WHO's criteria for cost-effectiveness in universal immunization.

Keywords

Rotavirus, cost-effectiveness, vaccination, breastfeeding, affordability.

Background

Despite the common practice of breastfeeding in developing countries, exclusive breastfeeding remains uncommon [1]. There is still a big challenge for healthcare professionals to encourage women to breastfeed exclusively. The World Health Organization (WHO) recommends exclusive breastfeeding for the first 6 months of life and continuing partially breastfeeding up to 2 years of age and beyond. Obviously, a focus both on initiating and continuing breastfeeding is very important to reduce the risk of failure on breastfeeding start and maintenance [2]. Yet, practice deviates from these recommendations. In particular, the low uptake of exclusive breastfeeding might be caused by the lack of breastfeeding support and education [3].

The WHO estimated that optimized breastfeeding would save 1.45 million children's lives each year in developing countries due to averting diarrhea and respiratory tract infections [4]. In Indonesia, rotavirus infection has been reported to be responsible for the majority of severe diarrhea in children under 5 years old, mainly in children aged between 6-24 months old [5]. Breast milk is considered to protect against rotavirus infection because it contains anti-rotavirus maternal antibodies and other nonspecific inhibitors [6]. Therefore, increasing breastfeeding promotion programs in Indonesia could be an alternative target to reduce the incidence of rotavirus diarrhea.

In terms of the health economic perspective, a previous study confirmed that implementation of rotavirus vaccination in Indonesia could be cost-effective [7]. Specifically, the previous study did not take breastfeeding explicitly into account and did not consider the effect of potential breastfeeding promotion interventions on cost-effectiveness of rotavirus immunization. Considering these limitations and the need of exploring the impact of breastfeeding promotion in childhood vaccination, we investigated the effect of breastfeeding promotion interventions on cost-effectiveness of rotavirus immunization in Indonesia, focusing on breastfeeding education and support intervention. Notably, optimized breast feeding might impact the economic evaluation results since maternal protection would be enhanced. Yet, cost-effectiveness could still be acceptable even in that situation. In this study we applied a cost-effectiveness model developed by University of Groningen labeled “Consensus Model on Rotavirus Vaccination” (CoRoVa), in the context of the Indonesian healthcare system for the next 5 years [8].

Methods

We applied the CoRoVa model, previously used to estimate cost-effectiveness of rotavirus vaccination both in developing and developed countries. The model is extensively validated and has the ability to calculate the potential impact of breastfeeding on cost-effectiveness of vaccinations. Considering a birth cohort of 4,200,000 infants [7] and using the data from the Indonesian Demographic and Health Survey (IDHS) on the age-specific breastfeeding patterns [9], we constructed an age-structured model with a 5-year time horizon based on breastfeeding statuses. In particular, we considered exclusive, partial or no breastfeeding as categories. In this study, we compared four scenarios: (i) base-case (I_0) reflecting the current situation for the population of under 5 years old, (ii) with an additional breastfeeding education intervention (I_1), (iii) with a support intervention on initiation and duration (I_2) and (iv) with both of these two interventions combined (I_3) (see Fig. 1). A time horizon of 5 years was chosen as rotavirus infection has been reported to be responsible for the majority of severe diarrhea in population under 5 years old in Indonesia, and severity rapidly decreases over 5 years [5]. Based on previous studies, each intervention could be plausibly assumed to increase the breastfeeding rate and correspondingly reduce the rotavirus-diarrhea incidence [1,3,10-12]. Aligning with the global health outcomes chosen in the previous study, we used the four levels for severity of rotavirus-diarrhea; *i.e.*, mild (home treatment), moderate (general practitioner treatment), severe (hospitalization) and death [13]. We ran the model in Microsoft Excel 2010 and used @ Risk 4.5.4 for probabilistic sensitivity analysis.

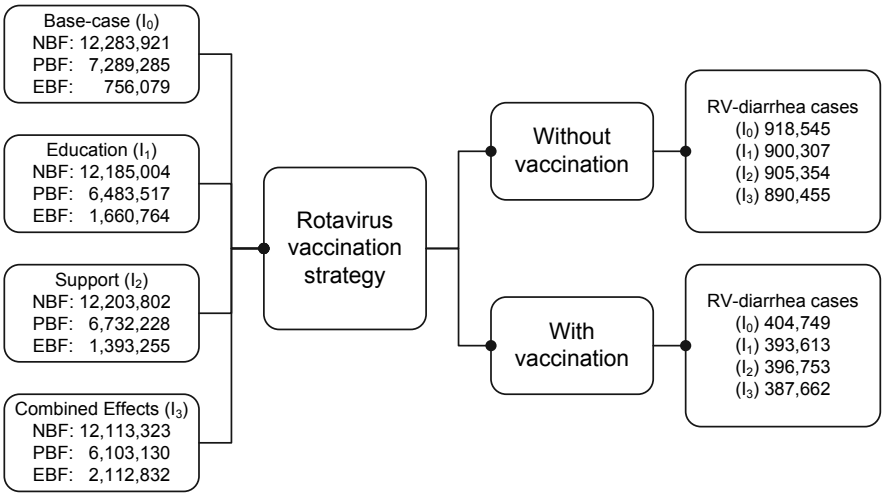

Fig. 1. Scheme for estimation of RV-diarrhea cases from all interventions

Applying the data from the 2007 IDHS on breastfeeding status by age and considering the WHO's recommendation on breastfeeding duration, we populated the under-5-year-old population in Indonesia into the relevant age groups (0-5, 6-11, 12-23, 24-35, 36-47 and 48-59 months) based on breastfeeding statuses: exclusive breastfeeding (EBF), partly breastfeeding (PBF) and no breastfeeding (NBF) [9,14]. We applied the actual distribution over the different breastfeeding modes in under-6-month-old population: 32.4% EBF, 59.1% PBF and 8.5% NBF [9]. For 6-11, 12-23 and 24-35 months, we applied the proportions of EBF:PBF:NBF at 3.1%:82.0%:14.9%, 0.3%:31.7%:68.0% and 0.1%:30.1%:69.8%, respectively [9]. For 36-47 months, the proportions were assumed to be 0%:10%:90%, and for 48-59 months, we assumed 100% NBF.

Due to the lack of data on 2011 diarrhea cases for under-5-year-old children in Indonesia, we estimated 2011 diarrhea cases over breastfeeding statuses by applying 2007 data on diarrhea cases and considering the WHO's data on relative risk of diarrhea morbidity by feeding statuses [15]. Additionally, we made the assumption that the same number of diarrhea cases as estimated for 2007 would overall apply to 2011 in Indonesia as well. Based on a 2009 study on economic evaluation of a routine rotavirus vaccination in Indonesia [7], we divided rotavirus-diarrhea cases into the respective levels of severity by using proportions of 76.0%, 22.9% and 1.16% for outpatient visits (moderate and mild cases), hospitalization (severe cases) and fatal cases. Additionally, we estimated that moderate cases would be 38.7% from mild cases [16]. These numbers would subsequently reflect the diarrhea cases in the base-case (I_0) in our study.

Assuming I_0 as a condition without breastfeeding promotion interventions in Indonesia, we compared it with three intervention scenarios as mentioned. Firstly, we assumed a breastfeeding education intervention (I_1). Based on the WHO's 2009 study in Iran [10], we assumed the same method and considered the same effect on increasing the rate of EBF. This method was initiated when a mother stayed for 24 hours in a postpartum ward [10]. Totally, it required a 40-hour-training during several days by a nutritionist on the advantages of breastfeeding and the importance of EBF [10]. On the initial day of discharge, the mother and her baby were observed on taking the right breastfeeding position, follow-up visits were done at days 10, 15 and 30 after delivery [10]. Considering the odds ratio (OR) on feeding patterns after 4 months delivery in the study and control groups between EBF (OR=16.89; 95%CI=5.42-52.59; p<0.0001), PBF (OR=0.22; 95%CI=0.10-0.49; p=0.0002) and NBF (OR=0.24; 95%CI=0.06-0.92; p=0.04) [10], we estimated the EBF-rate could be 120% higher than without an intervention on a 5-year time horizon. We assumed that the increasing rate of EBF reduces proportions of PBF and NBF at the same rates in each age group; *i.e.,* the

relative sizes of PBF and NBF remain the same as in I_0. We estimated the program could reduce rotavirus-diarrhea cases for under-5-year-old children by 2% [10,11,17].

Secondly, we analyzed a breastfeeding support intervention (I_2). This method has been applied among a group of low income women in the US, where they were trained and motivated on initiating and continuing to breastfeed and had to meet a lactation consultant individually to discuss breastfeeding during the pregnancy [3]. This method was followed-up at 4 days, 2-3-4-6 weeks, 3-4-5-6 months postpartum to ascertain on managing and continuing to breastfeed [3]. Applying the OR proportion of women breastfeeding after 6 months intervention [3] and considering the mean difference for education (I_1) and support (I_2) with three outcome measures (initiation, short-term and long-term duration) [18], we estimated the program could increase the proportion of EBF up to 84% higher as compared to no program and could reduce rotavirus-diarrhea cases for under-5-year-old children by 1.4% [3,11,15,18].

Thirdly, we assumed a combined effect of education and support interventions (I_3) [18]. We considered to apply the best effect between education, support and reported combined effects for initiation (mean difference=23%; 95%CI=12%-34%), short-term (mean difference=23%; 95%CI=12%-34%) and long-term duration (mean difference=23%; 95%CI=12%-34%), respectively [18]. We calculated the combined effect could increase the probability of EBF up to 179% higher as compared to no program and could reduce rotavirus-diarrhea cases for under-5-year-old children by 3% [3,11,15,18]. For all intervention scenarios (I_1, I_2 and I_3), we assumed the proportion of rotavirus-diarrhea cases on each age groups to remain the same as in I_0.

We assumed the Rotateq® vaccine in three doses to be used in our study. For formula-fed infants (NBF), we applied the rotavirus vaccine efficacies at 70%, 84% and 76.5% as initial vaccine effectiveness for mild-moderate, severe and fatal cases, respectively [7]. We calculated the vaccine efficacies for breastfed infants (EBF and PBF) at 63.1%, 75.7% and 68.9% for mild-moderate, severe and fatal cases, respectively, by considering the results from a study by Vesikari *et al.* on rotavirus vaccine efficacy in breast-fed European infants, and a comparative study on rotavirus vaccine efficacy in low, middle and high socio-economic settings by Lopman *et al.* [6,19]. Based on a previous study, we assumed that the vaccine effectiveness would exponentially decrease by 11% per year [20]. For between-dose efficacy, we applied 82% (between first and second doses) and 84% (between second and third doses) of full effectiveness [20,21]. We applied 2011 DPT vaccine coverage at 94% [22] as rotavirus vaccine coverage. We obtained the quality-adjusted-life-year (QALY) losses data by considering the disutility of each severity level and its duration from earlier works [16].

However, in this study we did not consider QALY-losses in caregivers.

In terms of economic perspectives, we analyzed the data both from healthcare and societal perspectives. In the healthcare perspective, we only considered direct medical costs, while in the societal perspective we considered broader cost items as well (direct medical, direct non-medical and indirect cost) [7]. We calculated all costs due to rotavirus-diarrhea for severe and moderate cases by considering 2007 data on hospitalization and outpatient visit costs due to rotavirus-diarrhea in Indonesia [7]. For mild cases, we estimated direct medical cost from the expenditure per child of oral-rehydration-therapy (ORT) in diarrhea treatment for children under 5 years old [23]. We converted these costs into 2011 US$ by considering the annual inflation rates.

Finally, we compared the reduction in rotavirus cases, QALY losses, and the cost-of-illness due to rotavirus-diarrhea. Using a market price of US$ 5 per dose [20], we estimated the incremental cost-effectiveness ratio (ICER) per QALY for all scenarios. Applying the WHO's definition on cost-effectiveness of universal immunization according to the GDP per capita, (i) highly cost-effective (less than one GDP per capita); (ii) cost-effective (between 1 and 3 times GDP per capita); and (iii) cost-ineffective (more than 3 times GDP per capita) [24], we specifically evaluated the results of rotavirus vaccination in Indonesia in all scenarios.

We performed univariate and probabilistic sensitivity analyses. Varying each parameter at value of ± 25% while keeping other parameters constant in univariate sensitivity analyses, we investigated the effects of different input parameters. Regarding the breastfeeding promotion interventions in this study, we varied from the minimal intervention (I_2) to the maximal intervention (I_3). Probabilistic sensitivity analysis (PSA) was performed by running 5000 Monte Carlo simulations. We evaluated the affordability related to the required budget for vaccination (vaccination costs + treatment costs) to analyze the budget impacts on the implementation of vaccination from the healthcare perspective, which are relevant for assisting decision makers in the health sector. All input parameters are shown in Table 1.

Table 1
Parameters used in the economic model

Parameters	Base-case value	Distribution	References
Vaccine coverage	94%	Triangular (89%; 94%; 99%)	[22]
Vaccine efficacy in formula-fed infants			
Mild	70.0%	Triangular (66.5%; 70.0%; 73.5%)	[7]
Moderate	70.0%	Triangular (66.5%; 70.0%; 73.5%)	
Severe	84.0%	Triangular (79.8%; 84.0%; 88.2%)	
Death	76.5%	Triangular (72.7%; 76.5%; 80.3%)	
Vaccine efficacy in breast-fed infants			
Mild	63.1%	Triangular (59.9%; 63.1%; 66.2%)	[6,7,19];
Moderate	63.1%	Triangular (59.9%; 63.1%; 66.2%)	calculated
Severe	75.7%	Triangular (71.9%; 75.7%; 79.5%)	
Death	68.9%	Triangular (65.5%; 68.9%; 72.4%)	
Rotavirus-diarrhea cases			
Base-case			
EBF	15,626	Normal (90%CI; 15,382-15,871)	[7,9,14,15,
PBF	452,658	Normal (90%CI; 451,412-453,903)	16,20];
NBF	450,261	Normal (90%CI; 449,018-451,504)	calculated
Education			
EBF	36,674	Normal (90%CI; 36,300-37,047)	[7,9,10,14,
PBF	420,264	Normal (90%CI; 419,058-421,469)	15,16,20];
NBF	442,056	Normal (90%CI; 440,824-443,289)	calculated
Support			
EBF	38,321	Normal (90%CI; 37,940-38,703)	[3,7,9,14,15,
PBF	422,586	Normal (90%CI; 421,378-423,795)	16,18,20];
NBF	441,548	Normal (90%CI; 440,316-442,780)	calculated
Combined Effects			
EBF	57,824	Normal (90%CI; 57,356-58,292)	[7,9,14,15,
PBF	394,543	Normal (90%CI; 393,371-395,715)	16,18,20];
NBF	433,441	Normal (90%CI; 432,220-434,663)	calculated
Utility losses			
Mild	0.00164	Triangular	[16,20]
Moderate	0.00548	(using 25% lower and upper)	
Severe	0.02110		
Death	1.00000		
Total medical direct costs per case (healthcare perspective, US$)			
Mild	1.08	Triangular (1.08; 1.44; 1.80)	[23]
Moderate	4.31	Triangular (3.23; 4.31; 5.39)	[7]
Severe	41.72	Triangular (31.29; 41.72; 52.15)	[7]
Total direct and indirect costs per case (societal perspective, US$)			
Mild	2.81	Triangular (2.11; 2.81; 3.52)	[23]
Moderate	5.69	Triangular (4.27; 5.69; 7.11)	[7]
Severe	56.34	Triangular (42.25; 56.34; 70.42)	[7]
Total vaccination and administration cost (per child, US$)			
3-dose, Market price	15.50	Alternative scenario	[7,20]
Discount rate	3%	Unvaried	[14,20]

Results

Assuming a vaccine coverage of 94% [22], vaccination of 4,200,000 infants [7] would reduce rotavirus-diarrhea with 513,796 cases in I_0. Considering the breastfeeding promotion interventions, vaccination would reduce rotavirus-diarrhea by 506,694; 508,601 and 502,793 for I_1, I_2 and I_3, respectively (see Table 2). From the societal perspective, vaccination would save US$ 8,369,236 in cost-of-illness due to rotavirus-diarrhea in I_0 and with breastfeeding promotion interventions it would save US$ 8,245,065; US$ 8,277,719 and US$

8,177,772 for I_1, I_2 and I_3, respectively. For QALYs loss, vaccination would save 348,887 discounted QALYs in I_0 and with breastfeeding promotion interventions it would save 343,534; 344,926 and 340,653 for I_1, I_2 and I_3, respectively

Table 2
Results from all interventions

	No Vaccination	Vaccination	Difference
Base-case (I_0)			
Number of RV-diarrhea cases [a,b]	918,545	404,749	513,796
Mild cases	503,190	243,800	259,390
Moderate cases	194,734	76,214	118,520
Severe cases	209,970	80,084	129,886
Death cases	10,651	4,651	6,000
QALYs lost [c]	616,904	268,027	348,887
Cost of illness (healthcare perspective) [c,d]	$ 9,887,025	$ 3,839,484	$ 6,047,541
Cost of illness (societal perspective) [c,e]	$ 13,748,048	$ 5,378,812	$ 8,369,236
Education (I_1)			
Number of RV-diarrhea cases [a,b]	900,307	393,613	506,694
Mild cases	493,198	237,539	255,659
Moderate cases	190,868	73,765	117,103
Severe cases	205,801	77,784	128,017
Death cases	10,440	4,525	5,915
QALYs lost [c]	603,799	260,265	343,534
Cost of illness (healthcare perspective) [g,h]	$ 9,681,360	$ 3,723,490	$ 5,957,870
Cost of illness (societal perspective) [g,i]	$ 13,462,069	$ 5,217,004	$ 8,245,065
Support (I_2)			
Number of RV-diarrhea cases [e,f]	905,354	396,753	508,601
Mild cases	495,963	239,315	256,648
Moderate cases	191,938	74,435	117,503
Severe cases	206,955	78,442	128,513
Death cases	10,498	4,561	5,937
QALYs lost [g]	607,368	262,442	344,926
Cost of illness (healthcare perspective) [g,h]	$ 9,737,646	$ 3,756,191	$ 5,981,455
Cost of illness (societal perspective) [g,i]	$ 13,540,335	$ 5,262,616	$ 8,277,719
Combined Effects (I_3)			
Number of RV-diarrhea cases [e,f]	890,455	387,662	502,793
Mild cases	487,802	234,175	253,627
Moderate cases	188,779	72,480	116,309
Severe cases	203,549	76,549	127,000
Death cases	10,325	4,458	5,867
QALYs lost [g]	596,795	256,142	340,653
Cost of illness (healthcare perspective) [g,h]	$ 9,571,093	$ 3,661,825	$ 5,909,268
Cost of illness (societal perspective) [g,i]	$ 13,308,742	$ 5,130,971	$ 8,177,772

[a] Population under 5 years old
[b] Undiscounted
[c] Discounted
[d] Direct medical cost
[e] Direct medical + direct non-medical + indirect costs

With a market price of US$ 5 per dose [20], cost-effectiveness values from the societal perspective are US$ 149, US$ 152, US$ 151 and US$ 153 for I_0, I_1, I_2 and I_3, respectively (see Fig. 2). The results are far below the 2011 Indonesian GDP per capita of US$ 3,495 [25]. Obviously, rotavirus immunization is a highly cost-effective intervention even assuming various breastfeeding promotion interventions according to the WHO's definition for cost-

effectiveness [24]. In particular, with an optimal breastfeeding promotion intervention (I_3), cost-effectiveness would increase to US$ 153 (societal perspective), yet the cost-effectiveness is still far below the WHO threshold.

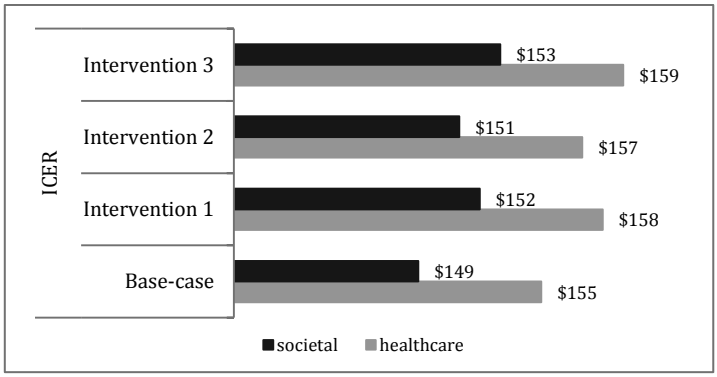

Fig. 2. Cost-effectiveness value for all interventions

The impacts of parameter changes on the ICERs are shown in a tornado chart (see Fig. 3). The results confirmed that the mortality rate and vaccine price were the most influential parameters in the sensitivity analyses. The cost-effectiveness results were not sensitive to the mild cost, moderate cost, severe cost, mild incidence, moderate incidence, severe incidence, breastfeeding promotions and vaccine efficacies.

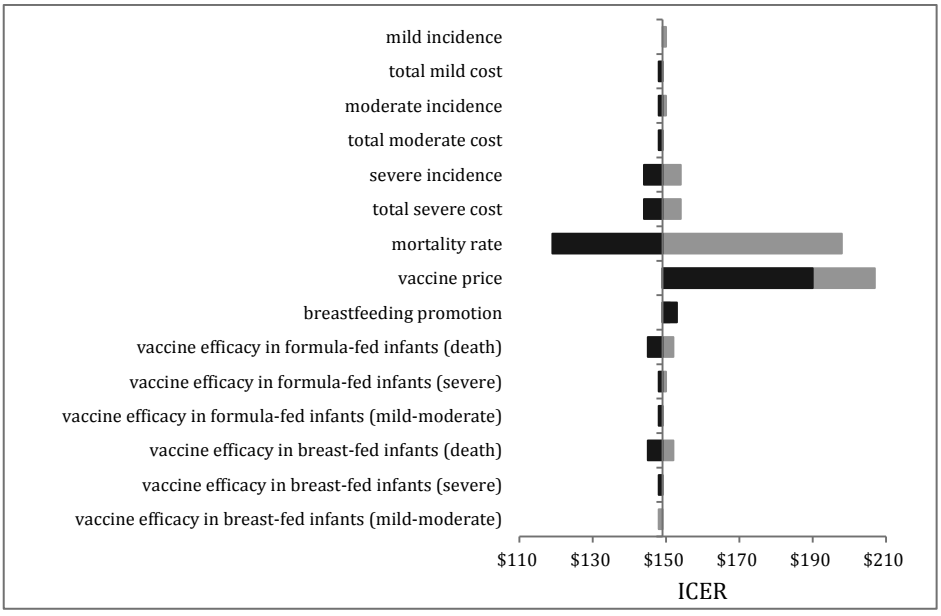

Fig. 3. Results of univariate sensitivity analyses

At a threshold ICER of US$ 149 (the base-case value from the societal perspective), the probability for the vaccination program to be cost-effective would be 59%; 9%; 19% and 2% for I_0, I_1, I_2 and I_3, respectively. Already at a threshold ICER of US$ 158, the probability for the vaccination program to be cost-effective would be 100% for all scenarios (see Fig. 4a). From the healthcare perspective, rotavirus immunization with a market price of US$ 5 per dose would always be implementable when the budget exceeds US$ 64,080,000; US$ 63,960,000; US$ 63,995,000 and US$ 63,905,000 for I_0, I_1, I_2 and I_3, respectively (see Fig. 4b).

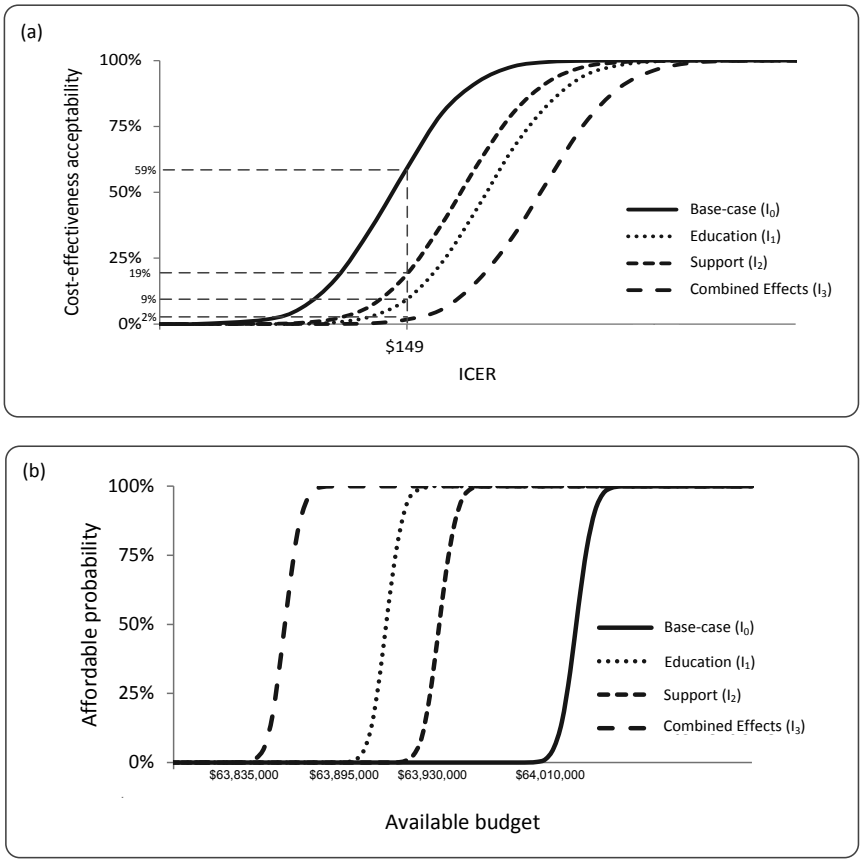

Fig. 4. Cost-effectiveness acceptability (the societal perspective) and affordability curves (the healthcare perspective)

Discussion

Compared to the base-case (I_0), breastfeeding interventions would increase EBF-rate by 120%, 84% and 179% for I_1, I_2 and I_3, respectively, as mentioned. At the market vaccine price of US$ 5 per dose, a rotavirus immunization program in Indonesia could reduce rotavirus-diarrhea by 259,390; 118,520; 129,886 and 6,000 for mild, moderate, severe and fatal cases, respectively. Assuming the base-case (I_0) as a condition without breastfeeding promotion interventions in Indonesia, breastfeeding promotion interventions could reduce rotavirus-diarrhea from I_0 by 1.4% - 3.1% for I_1, I_2 and I_3. From the social perspective, the incremental cost-effectiveness ratios are US$ 149; US$ 152; US$ 151 and US$ 153 for I_0, I_1, I_2 and I_3, respectively. Notably, our assumption that breastfeeding might decrease the effectiveness of rotavirus immunization is congruent with other studies [4,6,26]. Furthermore, based on the WHO's criteria for cost-effectiveness in universal vaccination, our results confirm that rotavirus vaccination would be a highly cost-effective public health intervention for Indonesia even under various breastfeeding promotion interventions [24].

In our study we took uncertainties into account by using univariate and probabilistic sensitivity analyses. The sensitivity analyses showed that the mortality rate and vaccine price were the most influential parameters impacting the cost-effectiveness results. The results on this study reconfirmed the results from previous study on cost-effectiveness of rotavirus immunization [16,27]. Postma *et al.* also found that the cost-effectiveness of rotavirus immunization in South East Asia Region (SEAR) was highly sensitive to the mortality rate and vaccine price [16]. Previously, a critical review on cost-effectiveness of rotavirus vaccination also mentioned mortality as the most influential parameter for middle and low-income countries [27].

We found a similar required funds (vaccination and treatment costs) for childhood vaccination. Considering the market vaccine price of US$ 5 per dose, rotavirus vaccination would require a budget of US$ 63,905,000 – US$ 64,080,000. Despite that all interventions require the same budget for the vaccination costs, the results indicate that breastfeeding promotion provides some potentials to reduce the treatment costs for rotavirus immunization in Indonesia due to its effect on reducing rotavirus-diarrhea cases. Breastfeeding promotion interventions would potentially result in less opportunities for cost offsets of vaccination. Compared to the total Indonesian government health budget for the whole immunization program in 2011 (US$ 198 million) [28], the required fund by the government for universal rotavirus vaccination would yet be unrealistic. Next to potentially manufacturing a rotavirus vaccine nationally at much lower costs prices, alternatively international support could be considered to achieve subsidized affordable prices.

Our study is not the first study on the economic analysis of rotavirus vaccination in Indonesia but it could provide crucial information for the policy makers specifically on the potential introduction of breastfeeding promotion coupled with the introduction of rotavirus immunization into the Indonesia National Immunization Programmes (NIP). This combined approach would increase the EBF-rate and reduce rotavirus-diarrhea cases at potential cost-effective efforts. We extended the CoRoVa model that has been used in a previous study to calculate cost-effectiveness of rotavirus for both developed and developing countries, by taking breastfeeding into account and investigating explicitly the effect of breastfeeding promotion interventions on cost-effectiveness of rotavirus immunization in Indonesia. The relationships between breastfeeding practice, breastfeeding promotion and rotavirus-diarrhea are well-known and therefore important to be included in our modeling approach. Despite that several other interventions on breastfeeding promotion were mentioned in a previous study [29], in this study we limited ourselves to two mostly-used interventions of breastfeeding education and support intervention.

We note several limitations in our study. Firstly, due to the lack of data on herd immunity, we had to apply a static model instead of a dynamic model. If we would have included herd immunity in a dynamic analysis there would be greater impacts of rotavirus vaccination and its cost-effectiveness would further improve. Secondly, we note the lack of 2011 data on rotavirus-diarrhea incidence in Indonesia and actual data on implementation of breastfeeding promotion interventions. We applied 2007 data on rotavirus-diarrhea incidence from a previous study and assumed it would be the same with 2011,while for the implementation of breastfeeding promotion interventions, we assumed that the base-case is a condition without specific breastfeeding promotion interventions in recent years. To overcome this limitation, we varied these assumptions extensively in multiple sensitivity analysis. Finally, we only obtained treatment costs for 2007 and we adjusted to 2011 values by considering the inflation rate.

Due to the low uptake of EBF in Indonesia and the high prevalence of rotavirus-diarrhea in population under 5 years old, policy makers in Indonesia could consider taking action to enhance the introduction of rotavirus vaccination and designing more intensive programs on breastfeeding promotion interventions. We showed that this approach is potentially highly cost-effective. However, as a developing country, Indonesia is faced with limited resources especially on providing the required budget both for implementation of rotavirus vaccination and breastfeeding promotion interventions. Getting funds from international organizations could be a realistic solution to overcome this problem. Hopefully, this study

assists the Indonesian government in designing optimal policies both to increase the EBF-rate and to reduce rotavirus-diarrhea incidence.

Conclusion

Rotavirus immunization is a highly cost-effective intervention for the Indonesian healthcare system even under various breastfeeding promotion interventions based on the WHO's criteria for cost-effectiveness in universal immunization. Nevertheless, the implementation of rotavirus immunization in Indonesia would be unrealistic without international organization support.

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CHAPTER 4

Cost-effectiveness of rotavirus immunization in Hangzhou, China: a comparison between two vaccines

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Maarten J. Postma

Accepted by Vaccine

Abstract

Objective

This study aims to more precisely assess the cost-effectiveness of rotavirus vaccination in Hangzhou, China, through an explicit comparison between two vaccines.

Method

An age-structured cohort model was developed for the 2011 birth cohort in Hangzhou. The model involves a 5-year time horizon with 1-month cycles for children less than a year old and annually thereafter. We made comparisons between use of the Lanzhou Lamb Rotavirus (LLR®) and Rotateq® vaccines. Monte Carlo simulations were used to examine the economic acceptability and affordability of rotavirus vaccination.

Results

At a vaccine price of US$ 23.20 per dose, implementation of the LLR® vaccine in Hangzhou would be a cost-effective intervention since the incremental-cost-effectiveness-ratios (ICERs) of US$ 11,863 and US$ 10,778 from the healthcare and societal perspectives were lower than the 2011 Gross Domestic Product (GDP) per capita in Hangzhou of US$ 12,447. For Rotateq®, at a vaccine price of US$ 86.67 per dose, implementation would be cost-ineffective since the ICERs were US$ 23,893 and US$ 22,770 from the healthcare and societal perspectives. From the healthcare perspective, vaccination would be 100% affordable under budgets of US$ 5,010,000 and US$ 16,983,000 for implementation of LLR® and Rotateq® vaccines, respectively.

Conclusion

Implementation of the LLR® vaccine in Hangzhou, China, could be a cost-effective intervention. Vaccine price and mortality rate were the most influential parameters impacting the ICERs.

Introduction

Rotavirus is the leading cause of severe diarrhea in children under 5 years old in both developed and developing countries [1,2]. This virus has also been reported to be responsible for approximately 40% of all severe gastroenteritis cases among children under 5 years old in China [3], which has the second highest number of rotavirus-related deaths in Asia, after India [4]. In China, only the Lanzhou Lamb Rotavirus (LLR®) vaccine has been used to prevent rotavirus infection [5]. LLR® is a live, orally administered vaccine, which is locally-manufactured by the Lanzhou Institute of Biological Products [6]. Since it received licensure from the Chinese government in 2000, approximately 30 million doses have been administered to Chinese children [5].

Located in East China, Hangzhou is one of the most developed areas in mainland China. Despite the fact that rotavirus has been responsible for 33.7% of the cases of acute childhood diarrhea in Hangzhou [7] up to now, no economic evaluation study on rotavirus vaccination has been specifically conducted in Hangzhou. To give an idea of the situation in another area in China, a cost-effectiveness analysis of rotavirus vaccination has been conducted in Zhengding, which confirmed that rotavirus vaccination could be a cost-effective intervention [8]. Compared with Hangzhou, Zhengding is a more impoverished area. Motivated by whether potential favorable cost-effectiveness remains within the context of different economic settings to justify full inclusion of the rotavirus vaccine into the National Immunization Programs (NIP), we conducted a cost-effectiveness analysis of rotavirus vaccination in Hangzhou, China, through an explicit comparison between two vaccines: LLR®, a locally-manufactured vaccine; and Rotateq®, one of the vaccines in the global market recommended by the World Health Organization (WHO).

Methods

Model

In this study we applied the CoRoVa model, an age-structured cohort model based on a decision tree, which has been used to assess the cost effectiveness of rotavirus vaccination in several countries. The model involves a 5-year time horizon with 1-month cycles for children less than 1 year old and annually thereafter [9,10]. Differing from previous studies on the same topic [7,8,11], we made a comparison between the use of the LLR® and Rotateq® vaccines. The model was run in Microsoft Excel 2010 and @Risk 4.5.4 was used for the probabilistic sensitivity analysis (see Figure 1).

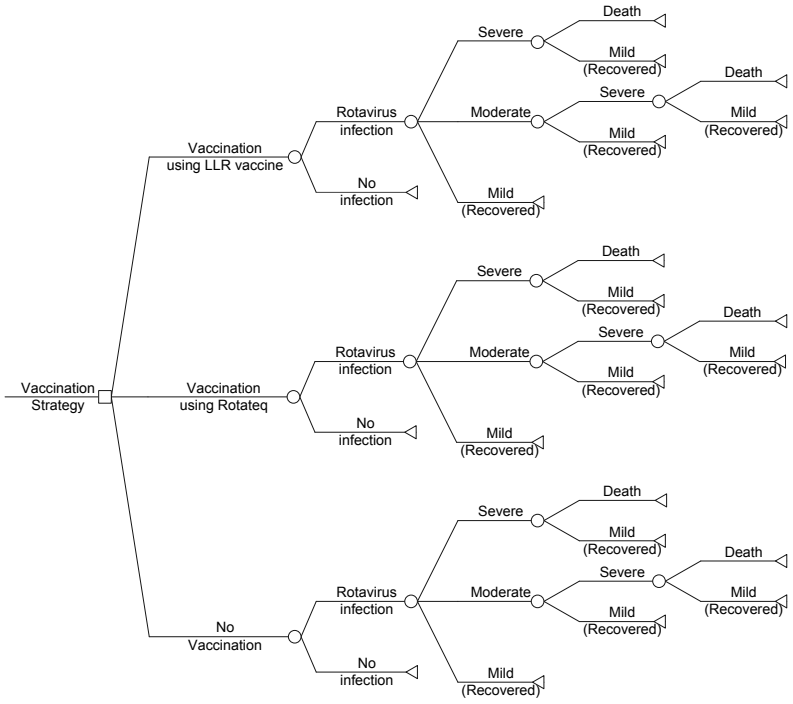

Fig. 1. Decision analytic model

Disease epidemiology estimates

We classified the rotavirus-diarrhea infection into four levels of severity, which have been generally used for global assessments: mild (home treatment), moderate (general practitioner treatment), severe (hospitalization) and fatal cases [1]. From a previous study on the epidemiology and economic burden of the rotavirus disease in Hangzhou in 2007-2008 [7], we obtained the number of moderate and severe cases in 2011 by dividing the number of outpatient and inpatient cases by two since the previous study was conducted over two years. We related these numbers of moderate and severe cases to the under-5-year-old population in Hangzhou, which was 350,000 according to the government census [7]. The number of moderate and severe cases in each age group was calculated by considering the positive rate of rotavirus in each age distribution [7]. For mild cases, we estimated the number of mild cases in each age group by applying the ratio of home treatment (mild) to outpatient cases (moderate), which was 4.5:1.0 according to Parashar's report on annual rotavirus incidence among children under 5 years old in developing countries [1]. Additionally, we used the mortality rate due to rotavirus infection for children under 5 years

old from the WHO's data in 2008 [12] (4,161 fatal cases attributed to rotavirus-diarrhea) to estimate the total number of rotavirus-related deaths in China (5 per 100,000) (see Table 1).

Vaccine characteristics

Rotateq® is administered in a 3-dose schedule at 2, 3 and 4 months of age. We estimated the effectiveness of the Rotateq® vaccine for severe and moderate cases to be 94.8% and 86 %, respectively, according to a study by Ruiz-Palacios *et al.* [11]. We further estimated the effectiveness of the Rotateq® vaccine in mild cases to be 81.3% by applying a ratio of vaccine effectiveness in mild to moderate cases of 52%:55%, which had been concluded from several studies [13-17]. For LLR®, the first dose would be administered at 2 months of age, while two other doses would be administered annually thereafter [6]. Due to the lack of data on vaccine effectiveness from the 3-dose scheduled LLR® vaccine, we applied a vaccine effectiveness of 44.2% for LLR® by taking the average vaccine effectiveness of the 1-dose (43.8%) and 2-dose (44.6%) scheduled vaccines [5]. There is no data separating the effectiveness of the LLR® vaccine for severe, moderate and mild cases, so we assumed that the ratios of vaccine effectiveness at each level of severity in LLR® would be the same as in Rotateq®. Additionally, the effectiveness against death was estimated to be the same as the effectiveness against severe cases for both vaccines.

In contrast to a previous study in Zhengding [8], we considered the in-between dose efficacy based on studies by Dennehy *et al.* [10] and Tu *et al.* [18]. To estimate in-between dose efficacy for Rotateq®, we utilized data from a previous study where the in-between dose efficacies were estimated to be 82% and 84% for between doses 1-2 and between doses 2-3, respectively [10]. Based on this data, we estimated vaccine effectiveness in mild cases between doses 1-2 to be 66.7% (82%×81.3%) and between doses 2-3 to be 68.3% (84%×81.3%). The same percentages of 82% and 84% were used to estimate between-dose efficacies for moderate, severe and fatal cases. For the LLR® vaccine, we also assumed the same effectiveness rates of 82% and 84% for between doses 1-2 and between doses 2-3, respectively. Based on a previous study conducted in rural China [8], the vaccine coverage in this study was assumed to be 90% for both vaccines (see Table 1).

QALY (quality-adjusted-life-year) loss

In this study, we applied discounted life expectancy when a child dies since QALY is the arithmetic product of life expectancy and a measure of the quality of the remaining life-years [19]. We used data on QALY losses provided by a number of comparable studies [14,15,20,21] with disutilities of 0.15, 0.25, 0.7 and 1.0 for mild, moderate, severe and fatal

cases, respectively, and durations of illness at 4, 8, 11 and 365 days for mild, moderate, severe and fatal cases, respectively. Based on those data, we estimated QALY losses for mild cases to be 0.00164 (4 × 0.15 / 365 days) [18]. We applied the same method to estimate QALY losses for moderate and severe cases. We did not consider caregiver QALY losses in our study (see Table 1).

Cost estimates

The analysis in this study was done from two perspectives, healthcare and societal perspectives. The Chinese government and patients were assumed to pay the healthcare and societal costs, respectively. In contrast to the healthcare perspective, which only includes direct medical costs, the societal perspective includes direct medical, direct non-medical (travel and other costs) and indirect costs (total caretaker's time cost = hours/days off work × estimated hour/day salary) [20]. We applied cost data from a previous hospital-based study on the economic burden associated with rotavirus diarrhea in eastern China [22]. Costs resulting from severe and moderate cases of rotavirus were estimated from inpatient and outpatient data, both for healthcare and societal perspectives. We estimated costs resulting from related mild cases of rotavirus by assuming the ratio of total cost associated with mild to moderate cases would be 4.6:5.1 and 8.7:10.7 for healthcare and societal perspectives, respectively, in line with a previous study using the same model in Vietnam [18]. Based on a 2012 study in China (LLR®) [5], and a 2009 study conducted in Taiwan (Rotateq®) [11], the prices of the vaccines were estimated at US$ 23.20 and US$ 86.67 per dose for the LLR® and Rotateq® vaccines, respectively. To estimate the price of Rotateq®, we had to use data from Taiwan instead of China since only the LLR® vaccine can be used in China. In this study, we did not consider the costs of potentially adverse events after rotavirus vaccination since adverse events are generally mild and it might be insignificant. All results from the analyses were converted to 2011 US dollars by using purchasing power parities (PPPs) and deflators as measured by the annual growth rate in the country-specific GDP implicit deflator [23,24] (see Table 1).

Table 1
Parameters used in the model

Parameters	Value	Distribution	References
Vaccine coverage	90%	90% (95%CI; 81.7%-98.9%)	[6]
Vaccine efficacy			
LLR®			
Mild	39.66%	39.66% (95%CI; 35.56%-43.53%)	[3,9];
Moderate	44.23%	44.23% (95%CI; 40.07%-48.57%)	calculated
Severe and death	48.72%	48.72% (95%CI; 43.59%-53.20%)	
Rotateq®			
Mild	81.31%	81.31% (95%CI; 73.95%; 89.24%)	[9];
Moderate	86.00%	86.00% (95%CI; 77.78%; 95.38%)	calculated
Severe and death	94.75%	94.75% (95%CI; 84.10%; 100.00%)	
Rotavirus-diarrhea cases (per 100,000 children)			
Mild	9,092	9,092 (95%CI; 8,914-9,270)	[1,7,8];
Moderate	2,012	2,012 (95%CI; 1,925-2,099)	calculated
Severe	209	209 (95%CI; 180-237)	
Death	5	5 (95%CI; 1-9)	
Utility losses			
Mild	0.00164	Beta (0-0.0003)	[10,13]
Moderate	0.00548	Beta (0-0.0018)	
Severe	0.02110	Beta (0-0.0089)	
Death	1.00000	Beta (0-1.0350)	
Total healthcare cost (US$)			
Mild	13.14	Gamma (6.37; 51.91)	[12,13,14,15]
Moderate	14.36	Gamma (7.76; 65.27)	[12,14,15]
Severe	471.93	Gamma (23,263; 33,699)	[12,14,15]
Total societal cost (US$)			
Mild	51.24	Gamma (193.15; 536.34)	[12,13,14,15]
Moderate	63.26	Gamma (308.18; 778.30)	[12,14,15]
Severe	702.16	Gamma (54,721; 74,089)	[12,14,15]
Vaccine price (per dose, US$)			
LLR®	18.88	Alternative scenario	[3,14,15]
Rotateq®	86.67	Alternative scenario	[9,14,15]
Discount rate	3%	Unvaried	[13]

Incremental cost-effectiveness ratio (ICER) analyses

The ICER was calculated to measure the outcomes from both healthcare and societal perspectives. Similarly to a previous study on the cost-effectiveness of the hepatitis A vaccination in China [25], cost-effectiveness criteria using the GDP-per-capita was used to evaluate the results of rotavirus vaccination in Hangzhou, China: (i) cost-effective (less than GDP per capita); and (ii) cost-ineffective (more than GDP per capita).

Sensitivity and budget impact analyses

In this study, we performed both univariate and probabilistic sensitivity analyses (PSA). Univariate sensitivity analyses were performed to investigate the effects of different input parameters by varying each parameter by ± 25% while keeping other parameters constant.

PSA were performed by running 5,000 Monte Carlo simulations using @Risk 4.5.4. The results of the PSA were presented in cost-effectiveness acceptability curves (CEACs) by using two thresholds, 1× GDP per capita and 3× GDP per capita. Based on the distribution of incremental costs and health gains from the same 5,000 Monte Carlo simulations, we evaluated the affordability of vaccinations with respect to the required budget (vaccination and treatment costs) from the healthcare perspective to describe the budget impacts on the implementation of rotavirus vaccination.

Results

Rotavirus-diarrhea cases and cost of illness

Assuming 90% vaccine coverage, vaccination of 350,000 children under 5 years old [7] would reduce rotavirus-diarrhea by 8,887 and 17,870 cases when vaccinating using LLR® and Rotateq® vaccines, respectively. In particular, the LLR® vaccine would reduce rotavirus-diarrhea by 6,967 mild cases; 1,719 moderate cases; 196 severe cases; and 5 fatal cases. Rotateq® vaccine would reduce rotavirus-diarrhea cases by 14,166 mild cases; 3,315 moderate cases; 379 severe cases; and 10 fatal cases. Rotavirus vaccination would save 351 and 678 QALYs losses when using the LLR® and Rotateq® vaccines, respectively. Furthermore, using the LLR® and Rotateq® vaccines would save US$ 580,223 and US$ 1,154,798 in costs, respectively, from the societal perspective (see Table 2a).

Cost-effectiveness analyses

The cost-effectiveness values from all perspectives are shown in Table 2b. At a vaccine price of US$ 23.20 per dose, the implementation of LLR® vaccine would yield ICERs of US$ 11,863 and US$ 10,778 from the healthcare and societal perspectives, respectively. Considering the 2011 GDP per capita in Hangzhou of US$ 12,447 [26], the results confirmed that rotavirus vaccination using LLR® vaccine would be a cost-effective intervention since the ICERs were less than GDP per capita. On the other hand, at a vaccine price of US$ 86.67 per dose, the ICERs for vaccination using Rotateq® vaccine were US$ 23,893 and US$ 22,770 from healthcare and societal perspectives, respectively. The results confirmed that rotavirus vaccination using Rotateq® vaccine would be a cost-ineffective intervention since the ICERs were much higher than GDP per capita.

Table 2.a
Results from all vaccination strategies

Vaccine	Without Vaccination	With Vaccination	Difference
LLR®			
Number of cases [a,b]	39,612	30,725	8,887
Mild cases	31,823	24,856	6,967
Moderate cases	7,041	5,322	1,719
Severe cases	730	534	196
Death cases	18	13	5
Cost of illness			
Healthcare perspective [c,d]	$ 819,144	$ 618,340	$ 200,804
Societal perspective [c,d]	$ 2,454,792	$ 1,874,569	$ 580,223
QALYs lost [c]	1,286	935	351
Rotateq®			
Number of cases [a,b]	39,612	21,742	17,870
Mild cases	31,823	17,657	14,166
Moderate cases	7,041	3,726	3,315
Severe cases	730	351	379
Death cases	18	8	10
Cost of illness			
Healthcare perspective [c,d]	$ 819,144	$ 422,702	$ 396,442
Societal perspective [c,d]	$ 2,454,792	$ 1,299,994	$ 1,154,798
QALYs lost [c]	1,286	608	678

[a] Undiscounted
[b] Population size: 350,000
[c] Discounted
[d] Costs are excluding vaccination cost

Table 2.b
Cost-effectiveness results

Cost-effectiveness of vaccination	LLR®	Rotateq®
vs no vaccination		
Net cost per QALY gained (healthcare)[a]	$ 11,863	$ 23,893
Net cost per QALY gained (societal)[a]	$ 10,778	$ 22,770

[a] Undiscounted

Univariate and probabilistic sensitivity analyses

The effects of different input parameters on the ICERs are shown in a tornado chart (see Figure 2). For both the LLR® and Rotateq® vaccines, the results showed that vaccine price and mortality rate were the most influential parameters in the sensitivity analyses. When the price of both vaccines fell by 50%, the ICERs also decreased sharply. In particular, both vaccines would have equal ICERs if the price of the Rotateq® vaccine fell by 45% and the price of the LLR® vaccine did not change.

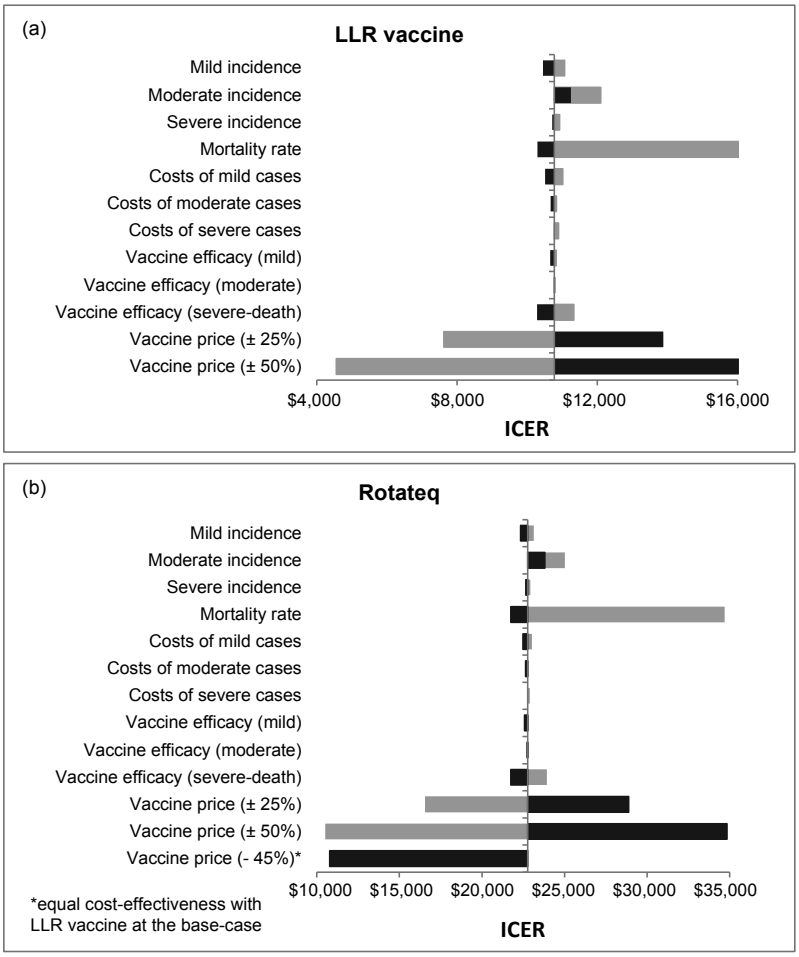

Fig. 2. Univariate sensitivity analyses from the societal perspective

The CEACs from the societal perspective showed that at the threshold ICER of US$ 12,447 (1×GDP per capita), the probability that implementation of rotavirus vaccination would be cost-effective was 69.68% and 0.52% for the LLR® and Rotateq® vaccines, respectively. If a threshold ICER of US$ 37,341 (3×GDP per capita) was used, the probability for the implementation of rotavirus vaccination to be cost-effective would be 99.98% and 94.94% for the LLR® and Rotateq® vaccines, respectively. The results confirmed that implementation of rotavirus vaccination in Hangzhou, China, would be cost-effective at different cost-effectiveness threshold values (see Figure 3a).

Affordability analyses

Figure 3b shows the affordability curves related to the required budget for vaccination from the healthcare perspective. At a budget of US$ 5,010,000 and US$ 16,983,000 for the implementation of LLR® and Rotateq® vaccines, respectively, rotavirus vaccination would be 100% affordable. On the other hand, it would not be affordable if the budget does not exceed US$ 4,925,000 and US$ 16,930,000 for the implementation of the LLR® and Rotateq® vaccines, respectively.

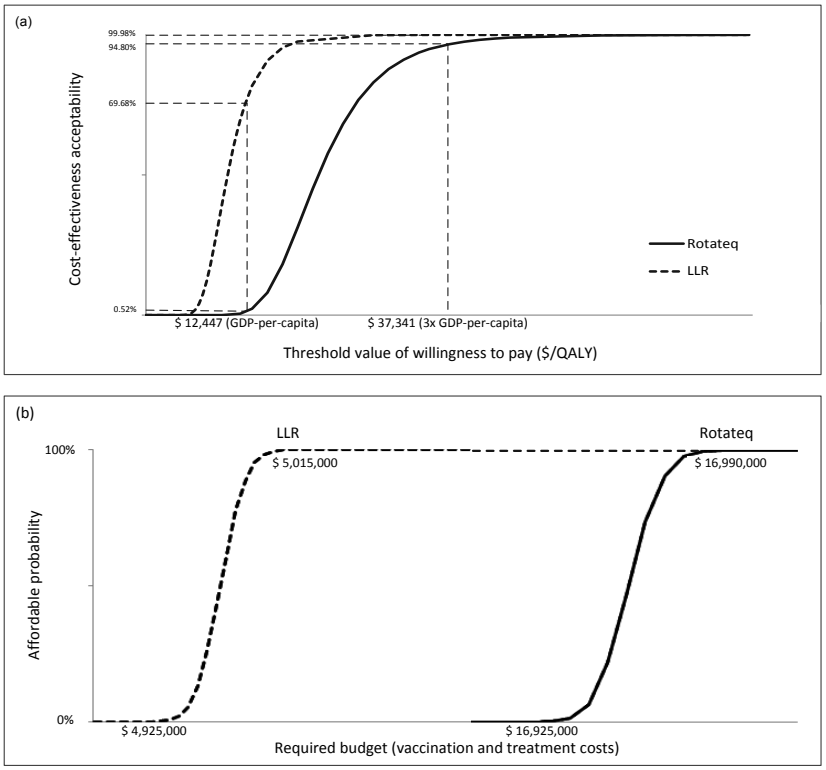

Fig. 3. (a) Cost-effectiveness acceptability curves from the societal perspective
(b) Affordability curves from the healthcare perspective

Discussion

Without vaccination, the rotavirus causes 39,612 cases of diarrhea among children under 5 years old. Applying a vaccine coverage of 90%, vaccination of 350,000 children would reduce rotavirus-diarrhea cases by 8,887 and 17,870 for vaccination with the LLR® and Rotateq® vaccines, respectively. The cost-effectiveness analyses yielded ICERs from the societal perspective at US$ 10,778 and US$ 22,770 for the LLR® and Rotateq® vaccines, respectively.

Our results confirm those of a previous study in Zhengding, which stated that implementation of the LLR vaccine could be a cost-effective intervention in China [8]. Our finding that implementation of the monovalent rotavirus vaccine (LLR®) would be more effective compared to that of the pentavalent vaccine (Rotateq®) also supports a previous study conducted in Taiwan [11]. This further warrants future attention on the implementation of the monovalent rotavirus vaccine. From an integrated health and economic perspective, implementation of the Rotateq® vaccine in China would be unrealistic. Despite the fact that implementation of a locally-manufactured vaccine appears to be more cost-effective than a global-market vaccine, more studies should be performed to further evaluate the safety and efficacy of the LLR® vaccine. Compared to the Rotateq® vaccine, which has been tested in major clinical trials in several countries [16,17], there has been only one post-licensing study on LLR® vaccine efficacy against severe rotavirus-diarrhea in China [6].

With respect to the progress on implementing rotavirus vaccination, it has been reported that many people cannot complete the recommended vaccination program of 3-doses of the LLR® vaccine because the price of the LLR® vaccine is relatively expensive [5]. In alignment with this, a study reported that the success of rotavirus vaccine implementation in many countries is expected to be associated with a decline in vaccine prices, which could be achieved by placing greater emphasis on price [27]. Furthermore, the sensitivity analyses in this study showed that vaccine price, together with mortality rate, were the most influential parameters impacting the ICERs. The results of this study confirm the results of a previous study by Postma *et al.,* which concluded that vaccine price and mortality rate would have substantial impacts on the cost-effectiveness of rotavirus vaccination in the Asia Region [9]. Potentially, our results indicate that, firstly, rotavirus vaccination in China could substantially prevent disease and, secondly, would be a more favorable intervention if vaccine price could be reduced significantly.

We do not present the first economic analysis of rotavirus vaccination in China. Compared to a previous study on similar topic in China [8], our study has used significantly different analysis techniques. Firstly, we explicitly compared two types of vaccine (LLR® and Rotateq®) in order to investigate the differences in results of cost-effectiveness, while previous studies used only one vaccine in their cost-effectiveness analyses. Secondly, we explicitly divided the outpatient cases into two different levels: mild (requiring home treatment) and moderate cases (requiring GP treatment). Thirdly, we took deaths associated with rotavirus into account, unlike a previous epidemiological study conducted in China.

Finally, we used an age-structured cohort model by considering in-between dose efficacy, waning immunity and the QALY loss so that results that would be more precise and valid.

Nevertheless, our study has some limitations. The first limitation is the use of a static model instead of a dynamic model that has the ability to incorporate the effects of herd immunity. However, even more favorable cost-effectiveness is theoretically predicted if we took herd immunity into account. The disadvantage of using a dynamic model is the requirement for a huge dataset because data from China are still scarce. Currently, only static models can realistically be used in such settings. The second limitation is the lack of data on LLR® vaccine efficacy for mild and moderate cases. We applied the same ratios of Rotateq® vaccine efficacy for severe, moderate and mild cases, thus the vaccine efficacy for LLR® might be over- or underestimated. The third limitation is the lack of specific epidemiology data on rotavirus-diarrhea in urban China. Because of this lack of data, we had to apply data from a previous study conducted in 2007 and to assume it would be the same in 2011. To adjust for this, we varied these estimates extensively in multiple sensitivity analyses. Finally, treatment costs were only available for 2007 and the costs had to be extrapolated for 2011.

In conclusion, with the second highest number of rotavirus-related deaths in Asia, China has a serious problem associated with a huge rotavirus disease burden. Implementation of rotavirus vaccination, which has been demonstrated to be a cost-effective intervention, should be urgently included into the NIP. Hopefully, this study will aid the Chinese government in making regulations to reduce the high risk of rotavirus infection in China, which is in line with WHO's goals for implementation of universal immunization.

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CHAPTER 5

Accelerating the introduction of rotavirus immunization in Indonesia

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Summary

The introduction of the rotavirus vaccine in Indonesia is currently in its infancy. Delay in its development might be caused by factors related to the perceived value of the vaccine, health system characteristics and policy considerations. Other factors, which may also interfere with optimizing the introduction, are financial barriers because Indonesia is a lower-middle-income country. Creating new fiscal space to finance new immunization programs, such as for the rotavirus immunization, is very important to ensure the sustainability of new programs so that such programs would be financed over the long term and not endanger the sustainability of the Indonesian government's financial position. This article provides an illustration of the various steps needed to accelerate the introduction of the rotavirus immunization.

Introduction

Introduction of new vaccines has been proven to be one of the most significant interventions in reducing childhood mortality. However, its implementation tends to be delayed in developing countries due to the lack of available data on disease burden and cost-effectiveness, inadequate health systems, financial barriers and insufficient concern from the government [1,2,3]. As a public-private partnership with the goal to accelerate the use of new and under-utilized vaccines, the GAVI Alliance (formerly known as the Global Alliance for Vaccines and Immunization) has supported affordable and financially sustainable introduction of new vaccines in developing countries by contributing a significant boost to global efforts to achieve Millennium Development Goal 4 (MDG 4), which specifically addresses the necessity to renew efforts against diarrhea [4].

The majority of cases involving severe diarrhea in children in Indonesia has been reported to be caused by rotavirus infection [5]. Thus, rotavirus vaccination has been recommended to be a priority by the World Health Organization (WHO) [6]. Several studies have confirmed that two leading rotavirus vaccines on the global market, Rotateq® and Rotarix®, are safe and efficacious for Asian infants [7,8]. In particular, two economic evaluation studies [9,10] concluded that rotavirus vaccination would be a highly cost-effective intervention in Indonesia, predicted to reduce 237,368 mild cases, 91,861 moderate cases, 117,110 severe cases and 5,450 deaths attributed to rotavirus diarrhea [10].

Nevertheless, Indonesia has not yet embarked upon implementation of rotavirus vaccination, being a lower-middle-income country with limited financial resources. To give an idea of the situation in other lower-middle-income countries, 19 lower-middle-income countries have introduced rotavirus vaccination in their National Immunization Programs (NIPs) as of June 2013, including 10 GAVI-eligible countries: Armenia, Bolivia, Georgia, Ghana, Guyana, Honduras, Moldova, Nicaragua, Sudan, and Yemen (see Table 1) [11,12]. Accelerating access to rotavirus vaccines is crucial since it would not only save the lives of Indonesian children but also reduce the tremendous economic and health burdens caused by the rotavirus disease. Motivated by the summary of evidence supporting introduction of rotavirus vaccination in Indonesia (see Table 2), we discuss the constraints and draw upon experiences from other countries to propose strategies that would help to accelerate the introduction of rotavirus immunization in Indonesia.

Table 1.
Introduction of rotavirus vaccination in lower-middle-income countries (as of June 2013)

Country	WHO Region	GAVI Eligible	Year	Vaccine
Armenia	EUR	Yes	2012	Rotarix®
Bolivia	AMR	Yes	2008	Rotarix®
El Salvador	AMR	No	2006	Rotarix®
Fiji	WPR	No	2012	Rotarix®
Georgia	EUR	Yes	2013	Rotarix®
Ghana	AFR	Yes	2012	Rotarix®
Guatemala	AMR	No	2010	Rotarix®
Guyana	AMR	Yes	2010	Rotateq®
Honduras	AMR	Yes	2009	Rotarix®
Iraq	EMR	No	2012	Rotateq®
Marshall Island	WPR	No	2009	Rotateq®
Micronesia	WPR	No	2011	Rotateq®
Moldova	EUR	Yes	2012	Rotarix®
Morocco	EMR	No	2010	Rotarix®
Nicaragua	AMR	Yes	2006	Rotateq®
Paraguay	AMR	No	2009	Rotarix®
Philippines	SEAR	No	2012	Rotarix®
Sudan	EMR	Yes	2011	Rotarix®
Yemen	EMR	Yes	2012	Rotarix®

AFR: African Region; AMR: America Region; EMR: Eastern Mediterranean Region; EUR: European Region; SEAR: Southeast Asia Region; WPR: Western Pacific Region.
Data taken from [11,12].

Table 2.
Key criteria for rotavirus-vaccine introduction in Indonesia

Elements	Summary of evidence	Ref.
Burden of rotavirus-diarrhea	Rotavirus reported as the most common cause of severe acute diarrhea among children under the age of 5 in Indonesia; identified as causal agent in 60% of children hospitalized with acute diarrhea and in 41% of children with diarrhea at outpatient clinics.	[5]
WHO position paper	Implementation of rotavirus vaccination should be a priority in countries with high mortality rates of rotavirus gastroenteritis (RVGE), such as countries in the South East Asia Region (SEAR) and sub-Saharan Africa.	[6]
Reported safety and efficacy of vaccines	Rotavirus vaccines (Rotateq® and Rotarix®) have been reported to be safe and effective for Asian infants.	[7,8]
Health benefit	Rotavirus vaccination would reduce rotavirus-diarrhea by 237 368 mild cases, 91 861 moderate cases, 117 110 severe cases and 5450 deaths.	[10]
Cost-effectiveness and public acceptance	Two previous studies confirmed rotavirus vaccination would be a highly cost-effective intervention. Compared to the 2011 Indonesian GDP per capita of US$ 3495, the incremental cost of rotavirus vaccination in Indonesia was much lower; only US$ 174 per quality-adjusted-life-year (QALY).	[9,10]
Affordability and required budget of rotavirus vaccination	With a budget of US$ 64,940,000 (2011 US$) for the market price of vaccine at US$ 5 per dose, vaccination would be completely affordable.	[10]
Introduction status in other SEAR countries	In 2012, the Philippines and Thailand introduced rotavirus vaccination to parts of their countries.	[11,12]
Introduction activities	Implementation of rotavirus vaccination is still in the pre-introduction phase.	[13]

Challenges to introducing the rotavirus vaccine in Indonesia

Based on a GAVI report, vaccine introduction activities can be divided into four phases: (i) pre-introduction, (ii) introduction, (iii) post-introduction and (iv) continuous activities [13]. Rotavirus vaccination in Indonesia appears to be in the first phase since there are still struggles over fundamental issues such as vaccine development, regulation and licensure; public health benefit; country readiness; vaccine supply chain planning; and long term financial planning [13]. Middle-income-countries are potentially the most unpredictable in terms of new vaccine adoption due to their increasing expenditure and growing system on health policy [2,14]. According to a previous study [2], delay in the introduction of new vaccines in middle-income countries, such as Indonesia, may be attributed to multiple factors, such as perceived vaccine value, health system characteristics and policy considerations.

Perceived vaccine value

Due to the lifelong protection that vaccines can provide in most cases [15], vaccination is one of the most cost-effective health interventions to save people's lives, improve health and ensure long-term prosperity. Over the long term, vaccination could even crucially boost the development in a country directly through medical savings and indirectly through economic benefits, such as cognitive development, educational attainment, labor productivity, income, savings and investment [16]. A GAVI report also stated that these economic benefits were produced at a remarkably low cost. Using data from GAVI-supported introductions of rotavirus vaccine during 2010 to 2015, it is realistic to estimate an 18% rate of return on such GAVI investments by 2020 [16]. Thus, vaccinating children against rotavirus infection can be categorized as one of the most valuable investments related to the diarrheal disease. These long-term returns on investment in vaccination are associated with savings, averted medical costs, averted deaths and productivity gains [16]. The perceived value of a new vaccine is an essential factor in setting priorities for new vaccines to be introduced into the NIP for the Indonesian government since implementation of rotavirus immunization would be unrealistic if the Indonesian government had to fully finance the endeavor without the supports of international organization. The required budget for universal rotavirus vaccination would be more than one third of the total health budget for the whole mandatory immunization program (hepatitis B, BCG, DTP, measles and polio) [10].

Health system characteristics

Immunization and the health system have a dynamic relationship since many aspects involved in an immunization system could also affect a country's health system and *vice versa* [17]. In particular, existing barriers and additional changes in health systems would likely impact the effect of immunization in a country [17]. An immunization program would not achieve a wide coverage without a strong and supportive health system in many countries [18]. Socio-cultural and demographic factors in a country may also significantly impact the introduction of new vaccines [19,20]. In Indonesia, decentralization and political reform in the late 1990s affected the sustainability of immunization funds [21]. The central government is now responsible for supplementary immunization activities, procurement of vaccines and syringes, technical assistance, development of guidelines, monitoring and evaluation, quality control and training [21]. The district governments support the central government by providing operational and handling costs [21]. Other health system characteristics can be critical factors in determining whether the proposed intervention would be accepted in a lower-middle-income country, such as immunization schedules, vaccine safety communication, options to locally produce the vaccine and cost [2].

Policy considerations

Using the introduction of the Haemophilus influenza type b (Hib) vaccine as an example, it could take approximately an additional 15 years to get a vaccine fully introduced into many developing countries [3,22,23]. The delay could even be longer in several developing countries due to their complicated policy-making systems [3]. These long time spans might be shortened by an integrated initiative to accelerate the introduction of a new vaccine in a country. Lessons learned from the introduction of the Hib vaccine, which could potentially impede the introduction of a rotavirus vaccine, include the negative impacts of lacking comprehensive recommendations, vivid financing policies and commitments from donors [3]. As the introduction of a new vaccine must be a part of the national plans and frameworks, policy considerations inherently play a crucial role. In Indonesia, recommendation for the introduction of a new vaccine into the NIP is made by the Indonesian Technical Advisory Group on Immunization (ITAGI), an independent body appointed by the Minister of Health consisting of a group of experts (pediatricians, policy makers, etc.) [24]. Therefore, the Indonesian government potentially already has an integrated system to add a new vaccine into the NIP. Despite this, the roles and responsibilities of centralized and decentralized levels of government are often unsynchronized and unclear in many cases. For instance, policy considerations in one district

may be different from other districts, even for a program as uniform in approach as immunization [25].

Rotavirus vaccination in Indonesia: resource needs, planning and budgeting

Generally, GAVI would involve a number of partners (WHO, UNICEF and World Bank) to accelerate rotavirus introduction in eligible countries, such as Indonesia. Each partner has different areas of priority areas in supporting GAVI's work. WHO's areas of priority are: (i) surveillance activities at the national and global levels; (ii) laboratory networks; (iii) monitoring and evaluation; and (iv) organizing training, meetings and personnel to support other activities [13]. UNICEF's assistance would be focused on cold chain storage, logistics management, communication, advocacy and social mobilization [13]. The World Bank would specifically support a country's operations for developing efficient and effective financing for general health and immunization [13].

Additionally, WHO, UNICEF and GAVI established guidelines in 2005 on developing a comprehensive Multi Year Plan (cMYP), which could assist countries in improving their immunization planning [26]. The aims of cMYP are to simplify various immunization planning activities at national levels, to reduce duplication of costs and to increase collaboration between national and regional planning [26]. Furthermore, the cMYP has cost-analysis and finance tools to estimate current and past costs to finance immunization programs, and to make projections for future resource requirements and financing gaps [26]. Given the Indonesian government's limited financial resources, however, the resource requirements and financing gaps reflected in the cMYP should be more fully integrated into the national health planning and budgeting frameworks, such as the annual or multi-year health budget. It should be taken into account that immunization programs in Indonesia have to share the government's limited resources with other priority health programs.

With approximately 4.8 million children [9] born each year in Indonesia with the potential risk of exposure to vaccine-preventable diseases, immunization financing is still considered as one of the most critical factors to reduce childhood death and disease. When introducing new vaccines, ensuring adequate and predictable financing is important because of the high cost of new vaccines [27]. The introduction of new vaccines might lead to a significantly higher scope and cost of NIPs in many countries. The World Bank reported that spending on immunization in fifty poor countries increased from US$ 6 to US$ 15 per infant in 2010, causing significant strains on health-care budgets [27], because of the introduction

of new vaccines, such as pentavalent, pneumococcal, rotavirus and human papilloma virus (HPV). Obviously, the increase in total financing for immunization would impact the sustainability of introducing new vaccines. In order to overcome this problem, several innovative financing mechanisms for supporting NIPs have been developed since 2000, such as through the International Finance Facility for Immunization (IFFIm) and the Advanced Market Commitments (AMCs) [27]. IFFIm was set up in 2006 to support GAVI's immunization program by accelerating the availability and predictability of its funds. With the World Bank as its treasury manager, IFFIm has transformed GAVI's financial landscape by nearly doubling GAVI's funding for immunization programs [27]. AMCs are mechanisms specifically designed to accelerate the introduction of new vaccines in developing countries by assuring that funds will be available to purchase vaccines once they have been developed and produced [27]. This mechanism has several key benefits, such as addressing current market failure, stimulating competition, encouraging lower vaccine prices and complementing a range of interventions [27].

In a country with limited immunization budgets, creating new fiscal space to finance new immunization programs, such as rotavirus immunization, is very important to ensure the sustainability of such new additional programs so that they would be financed over the medium and long term and in a way that would not endanger the sustainability of the Indonesian government's financial position. We designed a scheme for expanding fiscal space for rotavirus immunization in Indonesia (see Figure 1) based on literature [27,28]. We assumed that rotavirus immunization would be financed by the Indonesian government with external support from GAVI, WHO, UNICEF and the World Bank. New fiscal space for rotavirus immunization could be created from efficiency gains in other health interventions, other immunization programs and from the rotavirus immunization program itself. Expanding fiscal space could also be derived through new government financing from new revenue sources or from increased revenues, such as through economic growth, new tax administration and strengthened macroeconomic policies [28]. In particular, creating new fiscal space could be used for expanding both the NIPs and paying for the incremental costs of introducing new vaccines in Indonesia, including rotavirus vaccines [27].

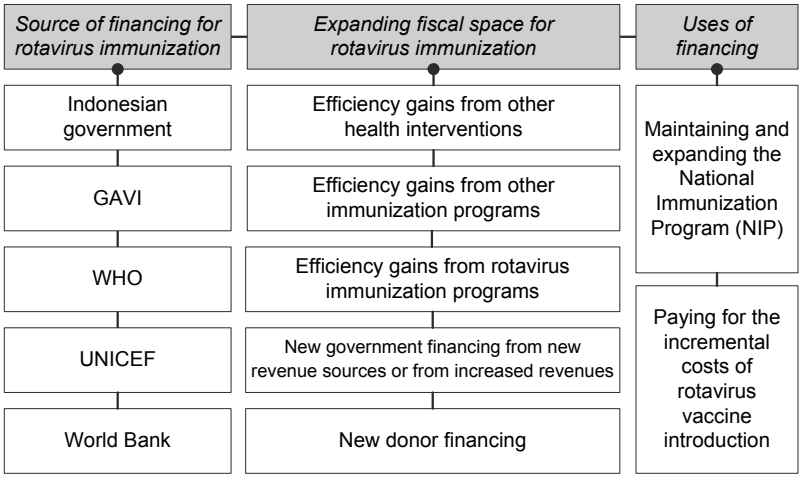

Figure 1. Expanding fiscal space for rotavirus immunization in Indonesia.
Data taken from [27,28].

Costs of accelerating rotavirus vaccine introduction in Indonesia

Although vaccines are one of the most cost-effective interventions in health care, financial barriers may interfere with the optimal introduction of new vaccines [29]. A study reported that acceleration in introducing new vaccines in developing countries are expected to be associated with a decline in vaccine prices, which could be caused by facilitating admission of new suppliers or by placing greater emphasis on price during procurement [30]. Considering a three-dose rotavirus vaccine (Rotateq®) and its market price (US$ 5 per dose) and GAVI-subsidized price (US$ 0.3 per dose) [10,31], the Indonesian government would require a budget of US$ 64,940,000 (market price) or US$ 10,175,000 (GAVI-subsidized prices) to implement rotavirus immunization for a vaccination coverage of 94% [10]. Additionally, as predicted by GAVI's data on the costs of accelerated vaccine introduction (AVI) of pneumococcal and rotavirus vaccines, the break-down of a country's costs for vaccine introduction by activity would be 61% for cold chain and logistics, 23% for training, 7% for communications, 6% for monitoring and evaluation, and 3% for operational and project management [13]. Using these data, we estimated vaccination cost by activity category for introducing rotavirus immunization in Indonesia for the fiscal year, 2012. Since budgets were available for 2011 prices, we converted them by using the annual inflation rate [32]. The resulting estimated costs per activity to introduce the rotavirus vaccine in Indonesia at market prices are shown in Table 3. Comparing the cost between base-line and accelerated rotavirus vaccine introductions, the total required budget for AVI would be US$ 39,834,143 more than that for the base-line. Considering the four introduction phases separately, the

required budget for AVI at market price would increase by US$ 9,808,853, US$ 12,987,322, US$ 8,610,310, and US$ 8,427,658 in the pre-introduction, introduction, post-introduction and continuous activities phases, respectively (see Table 4). In terms of financial sustainability plans, we calculated costs for three scenarios related to the required budget for vaccination in a 5-year time series based on different vaccine prices: (i) market price, (ii) GAVI-subsidized price, and (iii) GAVI-subsidized price for only the first 3 years, by assuming that vaccination coverage would increase 1.5% annually (see Figure 2).

Table 3
Vaccination costs by activity category (2012 US$)

Activity	Costs
Cold chain and logistics	22,007,445
Training	8,297,889
Communications	2,525,444
Monitoring and evaluation	2,164,667
Operational and project management	1,082,333
Total	36,077,778

Data taken from [10,13,32]

Table 4
Accelerated Vaccine Introduction (AVI) costs by phase (2012 US$)

Introduction phase	Costs by phase	AVI costs by phase
Pre-introduction	-	9,808,853
Introduction	35,093,293	48,080,615
Post-introduction	-	8,610,310
Continuous activities	984,485	9,412,143
Total	36,077,778	75,911,921

Data taken from [10,13,32]

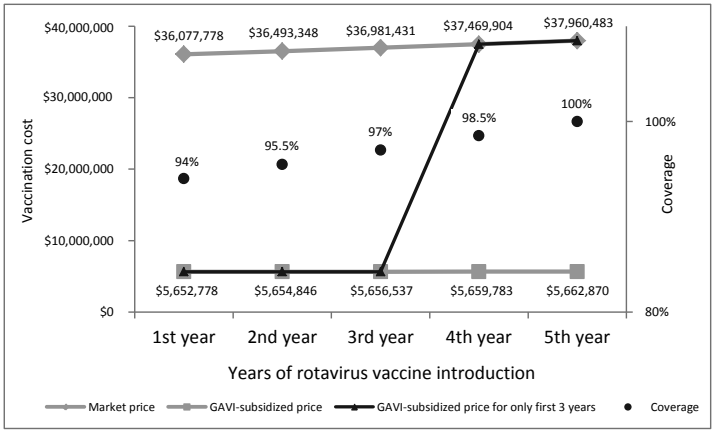

Figure 2. Vaccination cost and coverage over a 5-year time series
Data taken from [10]

Strategies to accelerate the introduction of rotavirus immunization in Indonesia

Research

Research and development of the rotavirus vaccine has been a high-priority target in the world during the last several years [33]. The relatively high price of rotavirus vaccines has been reported to be a barrier against implementing vaccination against rotavirus for lower-middle-income countries [24]. Regarding this problem, the pharmaceutical companies, GlaxoSmithKline (GSK) and Merck, took a laudable step towards addressing this barrier in June 2011 by announcing that they would make their vaccine prices more affordable for GAVI-eligible countries [34]. However, even at the drastically reduced rates, the cost of vaccinating children against rotavirus in Indonesia might remain prohibitively expensive. Furthermore, successful implementation of rotavirus vaccines would not only require the commitment of the Indonesian government to co-financing in the short-term, but also maintainance of the vaccine supply over the long-term. GAVI's support for rotavirus immunization will eventually end and the Indonesian government should be able to finance vaccination by itself in the future. To this end, the Indonesian government is already considering the manufacture of a rotavirus vaccine in mass production through Biofarma, the only vaccine manufacturer in Indonesia [35]. In collaboration with the Murdoch Children Research Institute (MCRI), Biofarma is developing RV3®, a new rotavirus vaccine from a unique strain of rotavirus that was found naturally in healthy asymptomatic newborn babies in Indonesia. These children were naturally protected from severe rotavirus diarrhea during the first two years of life [36]. This approach has enormous potential to reduce disease and childhood mortality around the world. Furthermore, the main idea behind this research collaboration is to provide more effective and affordable vaccines for Indonesian children; RV3® is being designed to be given orally to babies at birth to provide the earliest possible protection [36].

Communication

In many countries, communication and education activities have often been coupled with the introduction of new vaccines [37]. Socially introducing a new vaccination through mothers' clubs and professional organizations has been reported as part of successful efforts to ensure wide acceptance of Hepatitis B and Hib vaccine in several countries [38-42]. Providing knowledge and education about the disease and vaccine (*e.g.,* safety issues) also aided in the successful introduction of Hepatitis B and Hib vaccines [43-45]. Even in high-income

countries, such as the US and Canada, the HPV vaccine was actively marketed through direct consumer advertising and public awareness campaigns that targeted legislators and policy makers in addition to consumers [46]. Also in the UK, funding for media communication on meningococcal conjugate C vaccine was included in the budget for vaccine introduction [47].

With respect to the rotavirus vaccine, communication and education activities are essential in pointing out the characteristics of the rotavirus: it is highly contagious and spreads easily from person to person through contaminated hands and objects [48]. Mild rotavirus infections may be treated effectively by providing fluids and oral rehydration therapy. However, children with severe rotavirus diarrhea should be treated additionally by intravenous fluids in order to prevent dehydration. Because this type of emergency health care in developing countries is often inaccessible, preventing rotavirus infection through vaccination becomes even more critical in saving children's lives [48]. It should be clearly communicated that vaccination is still the best intervention to prevent severe rotavirus diarrhea because improvements in water quality, hygiene, and sanitation may stop bacteria and parasites that cause other types of diarrhea but they do not adequately prevent the transmission of rotavirus [48]. Life-saving rotavirus vaccines should be introduced as part of a comprehensive approach to control diarrheal disease within an integrated communication package, which identifies other interventions, such as oral rehydration therapy, breastfeeding, zinc treatment, and improvements in water and sanitation [48].

The influence of the media on vaccine decisions in Indonesia is quite limited and rarely mentioned [24]. However, the Indonesian government has used mass media, particularly television, to inform and raise public awareness on the rotavirus vaccine. The message could be sustained afterwards by the use of billboards, posters, banners and leaflets. Additionally, the Indonesian government has to respond to the anti-vaccination sentiment spreading rapidly through many channels in Indonesia [24] by using outreach campaigns. Despite the fact that the total coverage of the immunization program in Indonesia is more than 90%, movements against vaccines and immunization exist [49]. These movements mostly declare that the human body is naturally equipped with an immune system, which only needs boosting from natural sources [49]. Word has also been spreading that vaccines and immunization programs are just western conspiracies to weaken developing countries [49]. To approach this problem, the Indonesian government could consider involving influential religious groups, through the Indonesian Ulema Council (MUI), in socially introducing the need for vaccines and immunization.

Program coordination

As a GAVI-eligible country, the Indonesian government decided to expand the existing partnership with the GAVI Alliance in 2008 to improve routine infant immunization, and explicitly requested immunization service support for new and under-used vaccines, such as rotavirus vaccines [21]. When planning to include rotavirus vaccination into the NIP, coordination among the stakeholders in Indonesia is important to ensure the transition from policy to implementation. Vaccine introduction requires comprehensive planning and collaboration among the stakeholders involved, such as Ministry of Finance, Ministry of Health, ITAGI, vaccine manufacturers and international donors. The Ministry of Finance estimates the relative importance of introducing the rotavirus vaccine from their financial perspective and must take the relative cost-effectiveness of alternative spending into account. The Ministry of Health has to ensure the sustainability of current resource flow from external sources and expand to new sources of external financing. ITAGI should be persistent with their recommendations on the introduction of rotavirus vaccine and vaccine manufacturers' responsibilities are related to ensuring supplies for optimal coverage of the rotavirus immunization program. Finally, international donors would be focused on financial support to make important progress in accelerating the introduction of rotavirus vaccines in Indonesia.

Although the importance of leadership and appropriate governance on sustaining immunization efforts is now well recognized, this has proven to be one of the more difficult areas to address and has received the least attention in most of the funding proposals submitted to GAVI [43]. Learning from the successful introduction of the pentavalent vaccine (diphtheria-tetanus-pertussis (DTP), Haemophilus influenza type b (Hib) and hepatitis B), it should be emphasized that the type of cooperative and sustainable approach taken by the Indonesian government will be a key factor in reducing the global childhood mortality rate by two thirds by 2015 according to the MDG4 [50,51].

Lessons learned from the Philippines and Region of the Americas

Even though recent studies have shown that rotavirus vaccination can be cost-effective in the South East Asia Region (SEAR) [9,10,31,52-54], many countries in this region have yet to introduce the rotavirus vaccine into their NIPs. This reluctance may be caused by the uncertainty related to the cost of vaccine procurement [55]. However, the Philippines became the first country in SEAR to introduce the rotavirus vaccine in July 2012 [56]. Note that the Philippines have joined 18 other lower-middle-income countries in including rotavirus immunization in their NIPs [12]. Unlike Indonesia, the Philippines are not eligible

to apply for GAVI's support in co-financing vaccine introduction. Nonetheless, the Philippines took a stand against rotavirus infection, being motivated by the rapid and remarkable reductions in hospitalization and fatal cases due to rotavirus diarrhea in more than 30 countries that have introduced rotavirus vaccines into their NIPs. They focused on vaccinating children living in the poorest communities, which have the highest childhood morbidity and mortality rates from diarrheal disease [55]. Using the two-dose rotavirus vaccine (Rotarix®), which has been registered and approved by the Philippines' Bureau of Food and Drugs (BFAD), children were vaccinated before 6 months of age since the peak incidence of rotavirus diarrhea in the Philippines occurs at 6–24 months [57]. As the decline of severe and fatal diarrhea following the introduction of rotavirus vaccines leads to incredible potentials for saving children's lives in Asia and around the world, this announcement by the Philippines significantly encouraged other Asian countries, such as Indonesia, to intensify their considerations and efforts towards national introduction of rotavirus vaccines. In conclusion, the major point from the Philippines' experience is that in a country with limited resources, the government must exhibit serious political will to introduce the rotavirus vaccine.

In contrast to SEAR, 19 countries in the Region of the Americas have introduced rotavirus vaccine into their EPI as of June 2013 [11]. In Brazil, it has been reported that the introduction of rotavirus vaccine yielded approximately 1500 fewer deaths due to diarrhea and 130,000 fewer diarrhea admissions in children under 5 years old during 2007-2009 [58]. The number of severe diarrhea in Panama decreased by 22% and 37% in 2007 and 2008, respectively [59]. In Nicaragua, the number of gastroenteritis cases decreased by approximately 23% in children under 11 months old during the period of the rotavirus season [60], and hospitalization risk was reported to be 2 times lower among children vaccinated before the age of 12 months [61]. In general, the Pan American Health Organization (PAHO) has also succeeded in mobilizing additional sustainable funding to introduce rotavirus vaccines in its region [62]. There are several lessons to be learned from the introduction of rotavirus vaccines in the Region of the Americas, which can be applied to Indonesia. Firstly, due to the large packing size of rotavirus vaccines, cold chain storage should be ready before the introduction of rotavirus vaccine to minimize vaccine waste [62]. Secondly, it is important to evaluate the potential risk of intussusception after routine use of the rotavirus vaccine [63]. Since 2007, PAHO has collaborated with the United States Centers for Disease Control and Prevention (CDC) and PATH, an international nonprofit organization that transforms global health through innovation, to evaluate the use of Rotarix® related to the risk of intussusception in Brazil and Mexico [63]. Thirdly, the most crucial point is

related to age restrictions since rotavirus vaccination of children older than 24 months of age is not recommended [6]. To overcome this problem, the WHO recommended that Rotarix® should be administered in a 2-dose schedule at the time of DPT1 and DPT2 with a minimum interval of 4 weeks [6]. The vaccine, Rotateq®, should be administered in a 3-dose schedule at the same time with DPT1, DPT2 and DPT 3 with a minimum interval of 4 weeks between each dose [6].

Discussion

Despite the fact that broader interventions for diarrhea control have been given high priority in recent years, rotavirus diarrhea is still highly prevalent in developing countries. The use of rotavirus vaccination to prevent diarrhea is still not considered as a priority among policy makers in many developing countries, which may be caused by a lack of information and undervaluation of the rotavirus vaccines. Another major constraint for successful introduction of rotavirus vaccination concerns the underlying weakness of the health systems involved. In the context of new vaccine introductions, this article outlines the process of design and valuation, which could accelerate the introduction of rotavirus vaccines in Indonesia. It has been argued that accelerating the new vaccine introduction into ongoing immunization programs in developing countries is a commitment that is easily planned, but not easily implemented [64]. Following suggestions by GAVI, the Indonesian government could plan to introduce the rotavirus vaccination soon. However, this introduction could potentially be delayed since further comprehensive planning and collaboration among the stakeholders involved are still needed to ensure the transition from policy.

Compared to the price of other vaccines, such as the DTP vaccine (US$ 0.14 per dose), the price of rotavirus vaccines (US$ 5.15-7.50 per dose) is relatively high [65]. This could mean that procuring rotavirus vaccines would significantly exceed the health budgets of most governments in middle-income countries. As a lower-middle-income country, Indonesia would be supported by GAVI only over the short-term. Therefore, GAVI's goal, which is aligned with the introduction of rotavirus vaccines in GAVI-eligible countries, concerns accelerating a decrease in vaccine price. In this context, the Indonesian government may encourage the research and development to produce affordable rotavirus vaccines through Biofarma, as soon as possible within its jurisdiction, to guarantee the long-term sustainability of the vaccine supply when GAVI's support for rotavirus immunization eventually ends. Consequently, financial support seems a precondition to the implementation of rotavirus immunization into the NIP.

Financial factors play a key role in the introduction of new vaccines in all countries throughout the world for ensuring sustainable funding mechanisms and maintaining the optimal uses of existing vaccines. Continuing efforts by the Indonesian government, coupled with international donor contributions, are required to stimulate increased activity in both maintaining and expanding the NIP. For future pricing of the vaccine, a few assumptions on deriving the costs were needed based on GAVI's data related to the costs of accelerating introduction of the pneumococcal and rotavirus vaccines. These estimates of cost provide crucial inputs for analyses of cost-effectiveness. Given cost-effectiveness estimates, the Indonesian government should intensify their efforts towards national introduction of the rotavirus vaccine, especially since two studies have strongly suggested that rotavirus immunization would be cost-effective in Indonesia.

In conclusion, rotavirus immunization programs in Indonesia should be urgently implemented because they offer tremendous opportunities to prevent high morbidity and mortality associated with rotavirus diarrhea infection, and they could also explicitly reduce the tremendous economic and health burdens caused by rotavirus disease. Our aim in this article is to assist policy makers in deciding on an optimal strategy for accelerating the introduction of the rotavirus vaccine and, in particular, to reduce rotavirus diarrhea infection in Indonesia, through our systematic assessment of the issues involved.

Expert Commentary

Introduction of new interventions against infectious diseases, including the use of vaccines, is often strongly associated with less use of hospital services and lower hospital costs. Therefore, accelerating the introduction of new vaccines, such as those against the rotavirus, would be in line with several preventative efforts, such as lowering antibiotic use, reducing antimicrobial resistance and extending herd immunity and protection effects. Also, another important benefit to the health system facilitated by new vaccine introduction is the increase in awareness of improving disease surveillance.

In some cases, introduction of new vaccines required additional cold chain and logistic systems [66-70]. The introduction of rotavirus vaccines would indeed make more demands on cold chain capacity since the packing volume of rotavirus vaccines are approximately 7-18 times greater than the packing volume of DTP vaccines [65]. Consequently, it would require an additional cost to expand cold chain capacity. Vaccine manufacturers, including Biofarma, should consider their products' packaging and have initiatives to minimize the packing volume. In relation to the cost of rotavirus vaccines, creating more competition by specifically developing new rotavirus vaccines locally could reduce the price of rotavirus

vaccines in the future. This is important because GAVI subsidies for procuring rotavirus vaccines do not extend over a long period. Finally, to reduce vaccination cost, rotavirus vaccines can be co-administered with the majority of routine childhood vaccinations [71]. In particular, combining vaccines and utilizing existing infrastructure would significantly reduce the costs of accelerating rotavirus introduction in Indonesia.

In many developing countries, failures in introducing new vaccines were mostly caused by shortfalls in vaccine program funding. However, this problem could be resolved by strengthening internal financial systems and donor contributions. In the same way as GAVI requires from their eligible countries, they should prepare additional infrastructures and more effective vaccine management policies before they introduce a new vaccine. Also, WHO and UNICEF have developed a new communication framework for new vaccine introduction, focusing on new delivery technologies, readiness of cold chain storage, improvement of adapted vaccines and training of health care workers, which would be included in pre-introduction phase assessments. These requirements were designed to assure a country's systematic readiness when introducing new interventions and more specifically, to minimize failure due to economic factors.

Five-year view

Donor funding for immunization programs in developing countries is not always consistent or predictable. However, the introduction of new vaccines has created interest in the development of innovative funding sources and mechanisms for new vaccine introductions, and their sustainability. In the next five years, a number of new vaccines will be introduced and more funding mechanisms would likely be created to provide more stable vaccine financing. More precise assessment of disease burden and impact on morbidity and mortality would be required as a component of future evaluations to make a comprehensive Multi Year Plan (cMYP), especially in a country with limited health budgets, such as Indonesia.

It should be underlined that the implementation of rotavirus immunization in Indonesia is only one component in a comprehensive approach to prevent and control diarrheal disease. In order to achieve a continuous reduction in mortality related to diarrhea over the next five years, it is important to ensure a high coverage of rotavirus immunization after introduction, maintain the widespread use of oral rehydration therapy and continuously intensify efforts related to broader preventive interventions, such as sanitation improvement, hygienic foods campaign, water resources improvement and breastfeeding promotion.

Key issues

- Sustainability over the medium and long term are key issues in formulating a new health intervention.
- Financial factors play a key role in the introduction of new vaccines in all countries throughout the world for ensuring sustainable funding mechanisms and maintaining the optimal use of funds for existing vaccines and the broader health-care services.
- Delay in the introduction of new vaccines in middle-income countries, such as Indonesia, may be attributed to multiple factors, such as perceived vaccine value, health system characteristics and policy considerations.
- Creating new fiscal space to finance new immunization programs, such as for the rotavirus immunization, is very important to ensure the sustainability of new programs so that such programs would be financed over the long term and not endanger the sustainability of the Indonesian government's financial position.

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CHAPTER 6

Economic evaluations of hepatitis A vaccination in middle-income countries

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Summary

Economic evaluations of hepatitis A vaccination are important to assist national and international policy makers in different jurisdictions on making effective decisions. Up to now, a comprehensive review of the potential health and economic benefits on hepatitis A vaccination in middle-income countries has not yet been performed. In this study, we reviewed the literature on the cost-effectiveness of hepatitis A vaccination in middle-income countries. Most of the studies confirmed that hepatitis A vaccination was cost-effective or even cost-saving under certain conditions. We found that vaccine price, medical costs, incidence and discount rate were the most influential parameters on the sensitivity analyses. Vaccine price has been shown as a barrier for middle-income countries in implementing universal vaccination of hepatitis A. Given their relatively limited financial resources, implementation of single-dose vaccination could be considered. Despite our findings, we argue that further economic evaluations in middle-income countries are still required in the near future.

Introduction

Despite the small percentage of patients with hepatitis A virus (HAV) with severe conditions and potentially death, HAV infection caused major economic losses in many parts of the world in recent decades [1]. HAV is a non-enveloped virus with positive-stranded ribonucleic acid (RNA), classified into the hepatovirus genus of the picomavirus family [2,3], which can be transmitted from person to person, primarily by the faecal-oral route and the ingestion of contaminated food or drink [4]. Approximately 1.5 million cases of HAV infection occur annually with two different manifestation forms, usually asymptomatic in young children and mostly symptomatic in adults of which 85% reflect icteric symptoms [4,5,6]. The incidence rate of HAV is strongly and conversely correlated with the rising of socioeconomic status and the hygiene improvement of water resources [4,7,8]. Potentially, the most effective way to avoid HAV infection is through vaccination [9], which has been implemented in several countries, resulting in HAV reduction [10,11].

In 2000, the World Health Organization (WHO) started a campaign for the enhancement of hepatitis A vaccination programs by dividing regions based on three endemicity levels of HAV infection, *i.e.,* (i) low-endemic, (ii) intermediate-endemic, and (iii) high-endemic [12]. The endemicity level of HAV infection in a country is related to its hygienic condition and its sanitary infrastructure [13,14]. A previous study estimated that all high-income countries (HICs) have very low endemicity levels; most middle-income countries (MICs) have a mix of intermediate and low endemicity levels, and all low-income countries (LICs) have high endemicity levels of HAV [15].

In MICs with a mixture of intermediate and low prevalence, a substantial proportion of adolescents and adults is susceptible. As the severity of HAV infection increases with age, this might lead to a higher rate of severe conditions and death [12]. Furthermore, social developments (such as globalization, migration and travel patterns) increase the risk of transferring HAV from high-endemic (LICs) into intermediate-endemic (MICs) [16]. Therefore, it is relevant to evaluate the cost-effectiveness of hepatitis A vaccination programs in MICs, both regarding universal and targeted vaccination options. As a consequence of the increased role of economic evaluations in the last decade, systematic reviews of economic evaluations have become an essential tool in the policy making process recently [20-22]. Up to now, a comprehensive review of the potential health and economic benefits of hepatitis A vaccination in MICs has not been performed, whereas this information is important to assist national and international policy makers in different jurisdictions on making effective and rational decisions related to hepatitis A vaccination. Importantly, MICs are unlikely to receive as much financial assistance on vaccination programs as LICs do, in

the context of enhancing the relevance of economic analyses [20,21]. In this study, we review the literature on the cost-effectiveness of hepatitis A vaccination in MICs to evidence projected economic attractiveness of hepatitis A vaccination and possibly to provide recommendations on promoting HAV vaccination in such countries.

Methods

Literature search

We conducted a systematic search on January 7, 2013, to identify relevant articles in the last fifteen years (1998-2012) on economic evaluations of hepatitis A vaccination in three major databases: PubMed, Embase and LILACS. Reference lists were screened for title and abstract that included keywords. The search used variations of the following keywords: (hepatitis OR hepatitis A) AND (vaccin* OR immune*) AND (cost-minimi* OR cost-effectiveness OR cost-benefit OR cost-utility OR economic evaluation* OR economic analysis).

Selection criteria

In our study we used the following selection criteria regarding the topics:

- Study design should be complete economic evaluation, classified in one of the formal health-economic categories of cost-minimization analysis (CMA), cost-effectiveness analysis (CEA), cost-utility analysis (CUA) or cost-benefit analysis (CBA), being done in one of the MICs based on the country-classification data from the World Bank [23].
- Type of intervention should be universal childhood or targeted hepatitis A vaccination program.

Retrieved abstracts were independently screened by the research team (in particular, AAS and AR). We excluded incomplete economic evaluations, analyses of the combined hepatitis A/B vaccine, non-MICs' settings, systematic review studies, studies available in abstract only and studies which are not English. From the selected studies, we extracted both qualitative and quantitative data on title, authors, country, region (classified by the WHO), publication year, approach, sensitivity analysis, perspective, outcome, economic modeling, discount rates, vaccine costs, epidemiology of HAV, and vaccination strategies (universal or targeted). We classified studies into the four categories mentioned above: CMA, CEA, CUA or CBA. Economic results from the analyses were converted to 2012 US dollars by using purchasing power parities (PPPs) and deflators as measured by the annual growth rate in the country-specific GDP implicit deflator [24,25]. In the case when a study did not specify the year of cost, we assumed the year of cost would be the same as the year of publication.

Quality assessment

The quality of reporting was summarized in accordance to the recommendations by Beutels *et al.* on economic evaluations of viral hepatitis vaccination programs [22], and a study by S. Polinder *et al.* on the quality assessment of economic evaluations [26]. Appraisal items included study design, epidemiology estimates, vaccination, cost components, outcome measures and results. We applied these items for all included papers, as shown in Table 1.

Table 1
Criteria for assessing quality of economic evaluations [19,20]

Study design	Type of study Study perspective Discounting Time horizon of costs and benefits
Epidemiology estimates	Transparency on parameters used and assumptions Modeling study
Vaccination	Vaccination strategy Vaccination schedule Reporting of vaccine coverage Reporting of vaccine efficacy or vaccine effectiveness Reporting of annual rate of protective efficacy
Cost components	Reporting of direct medical, direct non-medical and indirect costs Reporting of productivity loss Reporting of vaccination cost Costing source
Outcome measures	Outcome measures stated Cost-effectiveness criteria
Results	ICERs (incremental cost-effectiveness ratios) Sensitivity analyses

Results

Literature search

The search yielded 235, 153 and 108 articles in PubMed, Embase and LILACS, respectively. We identified 456 articles after removing 40 duplicated articles from all sources. We selected articles by applying further eligibility criteria that studies should be strictly classifiable in one of the formal health-economic categories of CMA, CEA, CUA or CBA and having been done in one of the MICs based on the country-classification data from the World Bank [1]. We selected 19 articles after excluding 437 articles, of which 281 articles were clinical reports and epidemiological studies, 22 articles were focused on the combined vaccine, and 134 articles were not for MICs. From these 19 articles, we further excluded 10 articles as 6 articles were review studies, 3 articles were not written in English and 1 article was an incomplete economic evaluation. In total, there were 9 studies for final review (see Figure 1).

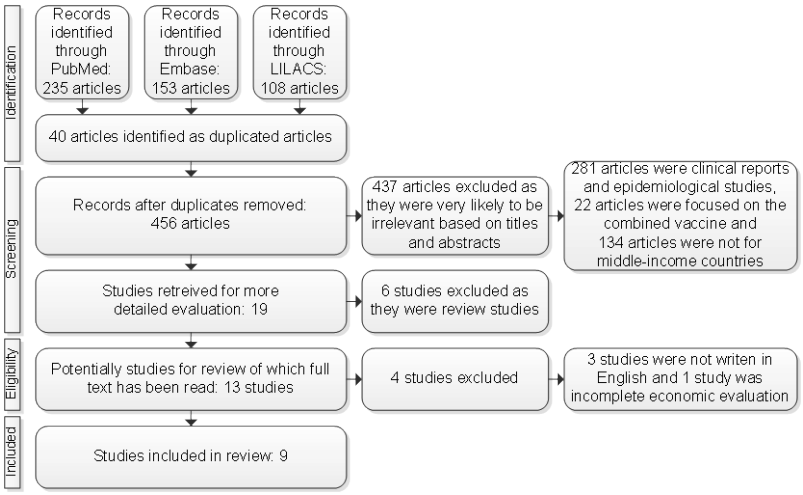

Figure 1. Flow chart for study selection

Study site characteristics

Our nine selected studies were from six different countries: Argentina (n=2), Brazil (n=1), Chile (n=2), China (n=1), Egypt (n=1) and Thailand (n=2) [27-35]. Egypt represented lower-middle-income countries (GDP per capita: US$ 1,026 to US$ 4,035), while Argentina, Brazil, Chile, China and Thailand represented upper-middle-income countries (GDP per capita: US$ 4,036 to US$ 12,475) [23]. From three levels of endemicity, only two levels were represented in this review, with seven studies in intermediate-endemic countries (Argentina, Brazil, Chile, China and Egypt) and two studies in the low-endemic country (Thailand) [36,37]. The oldest paper that appeared from our search was from 2002, focusing on the CBA of hepatitis A vaccination in Thailand, and the most recent one was from 2012 addressing the CEA of universal childhood hepatitis A vaccination in Brazil. The most relevant aspects of these studies are summarized in Table 2.

Table 2
Economic evaluations on hepatitis A vaccination in middle-income countries, as published in the international literature (2002-2012)

Study	Country	Classification of economy	Level of endemicity	Study objective	Detailed analysis	Type of study	Approach	Ref.
Sartori *et al.*, 2012	Brazil	Upper middle income	Intermediate	To conduct a cost-effectiveness analysis of a universal childhood hepatitis A vaccination program in Brazil	Comparison of cost-effectiveness between universal childhood hepatitis A vaccination in the second year of life and the current strategy (vaccination of high risk persons), in the low endemicity region (South and Southeast) and in the intermediate endemicity region (North, Northeast and Midwest)	CEA	Universal	[27]
El Karaksy *et al.*, 2008	Egypt	Lower middle income	Intermediate	To determine the prevalence of anti-hepatitis A virus (anti-HAV) antibodies and to calculate the cost-effectiveness of prescreening prior to hepatitis A	Comparison of cost-effectiveness between (i) vaccination on the adolescent group without screening, (ii) vaccination on the adolescent group after screening	CMA	Tergeted, children with CLD	[34]
Quezada *et al.*, 2008	Chile	Upper middle income	Intermediate	To evaluate the healthcare and economic impact of routine hepatitis A vaccination of toddlers in Chile	Comparison of cost-effectiveness between vaccination and non-vaccination	CEA	Universal	[29]
Zhuang *et al.*, 2008	China	Upper middle income	Intermediate	To evaluate whether universal childhood vaccination is advisable in China	Comparison of cost-effectiveness between vaccination (at ages 12 and 18 months) and non-vaccination, in the five regions defined by anti-HAV prevalence: the lowest, lower, intermediate, higher and the highest infection region	CEA, CUA	Universal	[33]
Ellis *et al.*, 2007	Argentina	Upper middle income	Intermediate	To investigate the cost-effectiveness of childhood vaccination against hepatitis A in the five geographic regions of Argentina, and to determine whether adding a second dose to the current one-dose schedule would provide health gains justifying its added cost	Comparison of cost-effectiveness between (i) vaccination at 12 months, (ii) vaccination at 12 and 72 months, (iii) vaccination at 12 and 18 months and (iv) non-vaccination	CUA	Universal	[30]
Lopez *et al.*, 2006	Argentina	Upper middle income	Intermediate	To evaluate the healthcare benefits and cost-effectiveness of a routine childhood vaccination program against hepatitis A in toddlers (between 1 year and school age) in Argentina	Comparison of cost-effectiveness between vaccination (at ages 12 and 18 months) and non-vaccination	CEA	Universal	[31]
Teppakdee *et al.*, 2002	Thailand	Upper middle income	Low	To simulate costs and benefits for persons in the context of hepatitis A prevention	Comparison of cost-effectiveness between (i) vaccination without screening, (ii) vaccination for those susceptible after screening for anti-HAV and (iii) non-vaccination	CBA	Universal	[33]
Soogarun *et al.*, 2002	Thailand	Upper middle income	Low	To determine the best strategy for Thailand, focused on the adolescent group (12-18 years of age)	Comparison of cost-effectiveness between (i) no intervention, (ii) vaccination without screening and (iii) vaccination after screening	CBA	Universal	[35]
Valuenzela *et al.*, 2001	Chile	Upper middle income	Intermediate	To assess the cost-effectiveness analysis of a universal childhood hepatitis A vaccination program in Chile	Comparison of cost-effectiveness between (i) vaccination at 18 and 54 months, (ii) vaccination at 18 and 24 months and (iii) non-vaccination	CEA	Universal	[28]

CEA: cost-effectiveness analysis; CBA: cost-benefit analysis; CMA: cost-minimization analysis; CUA: cost-utility analysis; CLD: chronic liver disease.

Assessing economic evaluation quality

Study design

Based on the economic summary measures, one study was classified as CMA, four as CEAs, one as CUA, two as CBAs and one as mixed CEA-CUA [26,38,39]. Regarding the perspective, five studies adopted the societal perspective and four studies adopted both the societal and healthcare perspectives. The societal perspective includes direct medical costs (*e.g.,* medical cost of outpatient and inpatient care, fulminant hepatic failure with or without liver transplantation, and follow-up of transplantation), direct non-medical costs (*e.g.,* transportation, food, etc.), and indirect costs (*e.g.,* productivity loss in patient and caregivers), often preferred to reflect the full public health impact [17,40]. Compared to the societal perspective, the healthcare perspective only includes direct medical costs, which are relevant for assisting decision makers in the health sector only [41].

Discounting deals with translating future values to current ones as the costs and consequences of a health technology generally might be spread out over multiple years [38]. Notably, current costs of hepatitis A vaccination program need to be compared to future benefits of prevented disease and reduced healthcare costs. As summarized in Table 3, four studies applied a 3% discount rate [28-31] and two studies applied a 5% discount rate [27,32]. Two studies did not report any discount rate since the cost and effect in these studies were calculated only for one year [34,35] and another study did not specifically report any discount rate [33]. The majority of the studies (n=7) used a long time horizon (24, 70, 72 and 100 years) [27-33] and only two studies used a short time horizon (1 year) [34,35]. Preference for a specific time horizon depends on the research question of the study, with time horizon potentially varying from a few weeks to several years or even the whole remaining life expectancy.

Table 3
Methodological characteristics of economic evaluations on hepatitis A vaccination in middle-income countries

Study	Methods and perspective	Herd protection	Time horizon (years)	Disc. rates (%)		Sensitivity analysis	Various parameters in the sensitivity analysis	Ref.
				Costs	Effects			
Sartori *et al.*, 2012	Dynamic model: an age and time-dependent Susceptible-Infected-Recovered-Vaccinated (SIRV) Perspective: healthcare and societal	Included	24	5	5	Univariate and bivariate	Frequency of icteric cases, hospitalization rate, proportions of liver transplantation, effective coverage, vaccine price, outpatient care cost and annual reduction in the force of infection	[27]
El Karaksy *et al.*, 2008	Perspective: societal.	Not included	1	ND	ND	ND	ND	[34]
Quezada *et al.*, 2008	Model: dynamic model, incorporate the changing epidemiology of hepatitis A and the development of vaccine-induced herd immunity Perspective: public payer and societal	Included	100	3	3	Univariate, multivariate, best-case and worst-case scenarios	Disease cost, discount rate, herd immunity, time frame, annual decrease and coverage rate	[29]
Zhuang *et al.*, 2008	Model: static (markov) model with single birth cohort Perspective: healthcare and societal	Not included	72	5	5	Univariate and multivariate	Vaccination coverage, vaccine protection, annual loss of vaccine protection, anuual decline of infection incidence, proportion of infection, hospitalization rate, case fatality rate, symptom duration, work loss duration, vaccination cost, medical cost, utility score, annual increase of per capita GDP and discount rate	[32]
Ellis *et al.*, 2007	Model: static (markov) model with single birth cohort. Perspective: societal	Not included	50	3	3	Univariate and multivariate	Duration of vaccine protection and vaccine price	[30]
Lopez *et al.*, 2006	Model: dynamic model, incorporate the changing epidemiology of infection and the impact of vaccine-induced herd immunity. Perspective: societal	Included	100	3	3	Univariate	Vaccination coverage, annual reductions in the force of infection, time horizon, discount rate,levels of herd immunity and disease cost	[31]
Teppakdee *et al.*, 2002	Model: static (markov) model with single birth cohort Perspective: societal	Not included	70	ND	ND	Univariate	Incidence rate, vaccine cost and with or without screening	[33]
Soogarun *et al.*, 2002	Perspective: societal	Not included	1	ND	ND	ND	ND	[35]
Valuenzela *et al.*, 2001	Model: static (markov) model with single birth cohort Perspective: healthcare and societal	Partially included	50	3	3	Univariate	Discount rate, medical cost, work loss cost, case fatality rate, duration of vaccine protection, vaccine dose and vaccine price	[28]

ND: not determined;GDP: gross domestic product

Epidemiological estimates

Local data related to the incidence and the force-of-infection were used in all studies. Based on the level of endemicity, Sartori *et al*. performed regional and nationwide CEAs [27] by applying hepatitis A seroprevalence data from nationwide population survey in Brazil and developing an age and time dependent susceptible-infectious-recovered-vaccinated (SIRV) dynamic model. Valenzuela *et al*. presented the incidence data and conducted both regional and national analyses in Chile by modifying an existing Markov model and considering infection index at 0.142, 0.163, 0.107, 0.102, 0.126 and 0.930 for people by age group at <6, 6-11, 12-17, 18-29, 30-39 and 40-49 years old, respectively [28]. In the similar way, Ellis *et al.* estimated the number of hepatitis A infections in Argentina by taking proportions at 7%, 37%, 71%, 76% and 86% for individuals by age group at <5, 5-9, 10-14, 15-49 and >49 years old [30]. In dynamic models, which incorporated the epidemiology changing and herd-immunity, Quezada *et al.* and Lopez *et al.* provided incidence cases and applied only nationwide CEAs in Chile and Argentina, respectively [29,31]. Using a Markov model, Zhuang *et al*. performed CEAs in five region in China: the lowest, lower, intermediate, higher and the highest prevalence regions by considering the anti-HAV prevalence values at the age of 12 months from the lowest to the highest infection region were 7.4%, 12.5%, 23.1%, 31.1% and 47.3%, respectively, and assuming an annual decline of 2% [32]. Teppakdee *et al.* adjusted the incidence data in 3 age groups (3-11, 12-18, and 19-40 years old) and conducted a nationwide CBA in Thailand by developing a Markov model and applying natural immunity of 9.4%, 15% and 70% for the three age groups, respectively [33]. Focusing only on a Thai adolescent group (12-18 years old), Soogarun *et al.* conducted a CBA by considering vaccination strategy with or without screening intervention [35]. El-Karaksy *et al.* carried out a study in 2004 in Egypt to analyze children with chronic liver disease (CLD) in a CMA study [34].

Most of the studies classified outcomes into four categories: outpatient cases (visits), inpatient cases, transplant cases, and deaths. Six studies [27-32] used epidemiological data from a previous study in the United States [37] to estimate the age-specific proportions of icteric cases of developing jaundice during acute hepatitis A and three studies did not take this parameter into account [33-35]. Additionally, four studies [29-32] applied the US data related to case-fatality [42,43], and five studies used case-fatality data from national studies to perform their estimations [27,28,33-35].

Most of the studies (n=6) applied static models, and only three studies applied dynamic models. Whereas its benefit is on potentially estimating more accurately, a dynamic model requires larger amounts of data, such as data on the annual changes in the force of infection

[29,31]. Comparing to static models, dynamic models are able to incorporate the epidemiology of hepatitis A, the development of herd immunity and potential age shifts incurred by the vaccination [44]. Notably, in a dynamic model, the probability of an individual to be infected depends on the contact with others and the distribution of infections in the population [45]. In our review, herd immunity was considered in three dynamic models [27,29,31] and partially included in one static model [28]. Considering herd immunity in the economic evaluation enhances the accuracy of cost-effectiveness of the vaccination program because the number of prevented cases would be captured more rigorously [46], although any age shift modeled in the dynamics might impact oppositely.

Vaccination

Depending on the level of endemicity and the fund availability for implementing hepatitis A vaccination, universal or targeted vaccination can be considered [47]. We identified eight studies on universal hepatitis A vaccination programs and only one study in Egypt analyzed targeted vaccination of children with CLD [34]. Prevention of HAV infection by universal vaccination has long been acknowledged to effectively reduce healthcare costs related to the disease and the effectiveness of universal HAV vaccination has been confirmed in many countries [29,31,48-51]. Implementing targeted hepatitis A vaccination is, however, still debatable regarding its effectiveness, in particular regarding its validity in adequately and completely targeting the groups of major interest [52-56].

All studies evaluated two doses vaccination strategies [27-35]. One study evaluated both one-dose and two-dose vaccination strategies [30]. Most studies considered vaccination of children up to 24 months of age and only two studies evaluated the strategy with a second dose at 54 and 72 months of age [28,30]. Three studies did not specify the vaccination schedule [33-35]. For vaccination coverage, six studies applied vaccine coverage of 66.5%-95% [27-32], and three studies did not specify the coverage [33-35]. Vaccine effectiveness was presented in several studies (n=8), ranging from 93-98% and 94-100% for first dose and second dose, respectively [27-33,35]. One study did not specifically report vaccine efficacy or vaccine effectiveness [34].

Only five studies considered the annual rate of decrease in protective efficacy in their studies [28-32]. Three studies [28,30,32] used data from a previous study in the United States [42], which was constructed by an expert panel. For the first 10 years, they applied an annual rate of decrease in protective efficacy at 1.62% and 0.31% for first dose and second dose, respectively, and after 10 years they applied increasing annual waning rates at 2.67% and 0.62% for first dose and second dose, respectively [42]. Two studies [29,31] used an

annual waning rate of seroprotection after vaccination at 0.58% by incorporating the seroprevalence data from the late 1990s [57] and the early 2000s [58]. Four studies did not take any decrease in the annual rate of protective efficacy into account [27,33-35] (see Table 4).

Table 4
Vaccine characteristics [17]

Study	Vaccination schedule	Coverage (%)		Efficacy (%)		Annual rate of protective efficacy (%)	Ref.
		1st dose	2nd dose	1st dose	2nd dose		
Sartori *et al.*, 2012	2 doses (12 or 15 months and 6 months after the first dose)	90	90	94	94	ND	[27]
El Karaksy *et al.*, 2008	2 doses	ND	ND	ND	ND	ND	[34]
Quezada *et al.*, 2008	2 doses (12 and 18 months)	95	95	95	100	0.58	[29]
Zhuang *et al.*, 2008	2 doses (12 and 18 months)	85	80	93	95	1 dose: 1.62 (1-10 years) and 2.67 (after 10 years) 2 doses: 0.31 (1-10 years) and 0.62 (after 10 years)	[32]
Ellis *et al.*, 2007	1 dose (12 months) or 2 doses (12 and 18 months or 12 and 72 months)	95	76 and 66.5	98	99	1 dose: 1.62 (1-10 years) and 2.67 (after 10 years) 2 doses: 0.31 (1-10 years) and 0.62 (after 10 years)	[30]
Lopez *et al.*, 2006	2 doses (12 and 18 months)	95	95	95	100	0.58	[31]
Teppakdee *et al.*, 2002	2 doses	ND	ND	96	96	ND	[33]
Soogarun *et al.*, 2002	2 doses	ND	ND	96	96	ND	[35]
Valuenzela *et al.*, 2001	2 doses (18 and 24 months or 18 and 54 months)	96	80 and 92.2	98	99	1 dose: 1.62 (1-10 years) and 2.67 (after 10 years) 2 doses: 0.31 (1-10 years) and 0.62 (after 10 years)	[28]

ND: not determined

Cost components

Direct medical, direct non-medical and indirect costs were considered in three studies [27,33,35]. One study only included direct medical costs [34] and five studies included both direct medical and indirect costs [28-32]. In the majority of studies, direct medical cost components were the medical cost of hepatitis A outpatient and inpatient care, fulminant hepatic failure with or without liver transplantation, and follow-up of transplantation. Most of the studies (n=8) used national data to estimate direct medical costs and only one study [29] applied international data to estimate direct medical costs. Based on previous studies in US [59], Valenzuela *et al*. and Ellis *et al.* considered the lifetime cost of graft maintenance for liver transplant patients, which was estimated to cost more than the transplant procedure itself [28,30]. Among eight studies, which included indirect costs [27-33,35], five studies calculated the productivity loss due to HAV infection for patients [28,30,32,33,35], while two studies also included the productivity loss of caregivers [27,29]. Additionally, the productivity losses in five studies were calculated by incorporating the daily gross-wage-rate in each country [27-31]. Furthermore, three studies used per-capita gross domestic product (GDP) to estimate the work loss costs due to HAV infection [32,33,35]. Sartori *et al*. estimated the number of lost workdays of 15 days and 24-30 days for outpatients and inpatients, respectively [27]. Zhuang *et al*. determined work loss durations of 16, 33 and 40 days for non-hospitalized, hospitalized and ultimately fatal cases, respectively, in their CEA-CUA study [32]. Valenzuela *et al.* and Ellis *et al.* argued that the mean duration of work loss would be 28 days [28,30], based on studies from the United States [60] and Israel [45]. Quezada *et al*. estimated work loss of 3 and 25 days for patient ≤15 years old and older patients, respectively [29]. Teppakdee *et al.* and Soogarun *et al.* conservatively assumed that the work-day-loss were due to hospitalization period only [33,35]. Lopez *et al.* did not specify the indirect costs due to HAV infection in their study [31]. Regarding the vaccination cost, all studies [27-35] included the vaccine price per dose and five studies [27-30,32] additionally included the administration cost. Most of the studies did not consider costs of potential adverse events (AE) after hepatitis A vaccination since AEs are generally mild and it might be insignificant. Only one study took the vaccine cost related to AEs into account [29] (see Table 5).

Table 5
Cost elements of economic evaluations on hepatitis A vaccination in middle-income countries

Study	Cost elements	Ref.
Sartori *et al.*, 2012	Direct medical costs: outpatient care, inpatient treatment, liver transplantation Direct non-medical costs: transportation Indirect costs: productivity loss due to hepatitis A by the patient or caregiver (mother) of children aged <15 years Vaccination costs: vaccine price per dose, administration cost	[27]
El Karaksy *et al.*, 2008	Direct medical cost: cost of a single test of anti-HAV antibodies Vaccination costs: vaccine price per dose	[34]
Quezada *et al.*, 2008	Direct medical costs: outpatient medical cost, hospitalization cost, fulminant hepatic failure with liver transplantation Indirect costs: parental work loss for patients ≤ 15 years old, stick leave for patients > 15 years old Vaccination costs: vaccine price per dose, administration cost, adverse events cost	[29]
Zhuang *et al.*, 2008	Direct medical costs: non-hospitalized case, hospitalized case and death case Indirect costs: productivity loss in patients 18-59 years old (16, 33 and 40 days for non-hospitalized, hospitalized and fatal cases) Vaccination costs: vaccine price per dose, administration cost	[32]
Ellis *et al.*, 2007	Direct medical costs: medical costs of hepatitis A outpatient, hospitalized patient without acute liver failure, hospitalized patient with acute liver failure and liver transplant patient Indirect costs: 28 days of productivity loss in patients > 17 years of age Vaccination costs: vaccine price per dose, administration cost	[30]
Lopez *et al.*, 2006	Direct medical costs: laboratory tests, IgM administration, outpatient medical visit, hospitalization costs, fulminant hepatic failure with and without liver Indirect costs Vaccination costs: vaccine price per dose	[31]
Teppakdee *et al.*, 2002	Direct medical costs: serology test, medical cost/visit, outpatient, hepatitis A without complication, with cholestatis and with fulminant liver failure Direct non-medical costs: transportation in patients 3-11, 12-18 and 19-40 years old Indirect costs: work day loss in patients 3-11, 12-18 and 19-40 years old Vaccination costs: vaccine price per dose	[33]
Soogarun *et al.*, 2002	Direct medical costs: drug and hospitalization cost Direct non-medical costs: transportation Indirect costs: cost in loss of productivity relative to net income per capita per year	[35]
Valuenzela *et al.*, 2001	Direct medical costs: medical costs of hepatitis A outpatient, hospitalized and liver transplant Indirect costs: 28 days of productivity loss in patients 20-59 years of age Vaccination costs: vaccine price per dose, administration cost	[28]

Outcome measures

Three economic summary measures were applied in nine selected studies: (i) net cost or cost of illness (COI) [34]; (ii) net benefit or cost benefit to cost ratio [33,35]; (iii) cost per life year saved [27,29,31]; and (iv) cost per quality-adjusted-life year (QALY) [28,30,32]. The majority of the studies (n=7) confirmed that the implementation of hepatitis A vaccination would be a

cost-effective intervention [27-32,34]. Moreover, four studies estimated that vaccination would be a cost-saving intervention [27,28,30,32]. All CBAs confirmed that vaccination would not be an actual cost beneficial intervention [33,35].

Regarding the cost-effectiveness criteria, five studies [28-32] used a conventional consideration that an intervention would be cost-effective if the ICER does not exceed the GDP per capita [61]. Only one study [27] used the WHO's definition on cost-effectiveness of universal immunization according to the GDP per capita, whether an intervention would be highly cost-effective (less than one GDP per capita), cost-effective (between 1 and 3 times GDP per capita) or cost-ineffective (more than 3 times GDP per capita) [62]. Other three studies did not apply the cost-effectiveness criteria as they were CMA and CBA studies [33-35].

Interpretation of results

Table 6 presents the results of studies. Sartori *et al.* showed that universal childhood hepatitis A vaccination would be a cost-saving strategy in intermediate and low endemic regions and Brazil in general from both the healthcare and societal perspectives [27]. The result was in line with a similar previous study in the context of comparing the current strategy (vaccination of high-risk groups) with universal vaccination [63]. In the absence of Brazilian guidelines on cost-effectiveness, Sartori *et al.* used the WHO criteria for cost-effectiveness of universal immunization and the GDP per capita as the threshold [27,64]. Sensitivity analyses indicated that the proportion of icteric cases and the outpatient costs were the most influential on the incremental cost-effectiveness ratio (ICER) [22]. The vaccine price per dose also had a major impact on the ICER [27]. Even with an increase of 50% of vaccine in the base-case, vaccination remained a cost-saving intervention. Notably, compared to other cost-effectiveness studies of new vaccines (rotavirus, varicella, pneumococcal and meningococcal C conjugate) in Brazil, only hepatitis A vaccination could be confirmed as a cost-saving intervention [38,65,66].

Table 6.
Primary results (2012 US$) [17]

Study	Vaccination cost (2012 US$)		Primary results	Ref.
	Vaccine price per dose	Administration cost		
Sartori *et al.*, 2012	US$ 7.9	US$ 1.1	Healthcare perspective: cost-saving. Societal perspective: cost-saving.	[27,24,25]
El Karaksy *et al.*, 2008	US$ 15.0	ND	Children with CLD > 2 years old are recommended to be vaccinated. Prescreening in the group with CLD > 5 years old would be cheaper than in < 5 years old.	[34,24,25]
Quezada *et al.*, 2008	US$ 8.0	US$ 0.3	Vaccination at 12 and 18 months: US$ 3,625/QALY gained.	[29,24,25]
Zhuang *et al.*, 2008	US$ 2.4	US$ 0.3	Healthcare and societal perspective: cost-saving. The highest region vaccination would need additional cost at US$ 149 and US$ 201 per QALY gained from the healthcare and the societal perspective, respectively.	[32,24,25]
Ellis *et al.*, 2007	US$ 6.2	US$ 0.3	Vaccination at 12 months: cost-saving. Vaccination at 12 and 18 months: US$ 401/QALY gained. Vaccination at 12 and 72 months: US$ 690/QALY gained.	[30,24,25]
Lopez *et al.*, 2006	US$ 5.8	ND	Vaccination at 12 and 18 months: US$ 2,838/QALY gained.	[31,24,25]
Teppakdee *et al.*, 2002	US$ 87* (3-11 and 12-18 years old); US$ 136* (19-40 years old.)	ND	Benefit of vaccination without screening: -US$ 119 (3-11 years old); -US$ 126 (12-18 years old) and -US$ 309 (19-40 years old). Benefit of vaccination with screening: -US$ 186 (3-11 years old); -US$ 177 (12-18 years old) and -US$ 164 (19-40 years old).	[33,24,25]
Soogarun *et al.*, 2002	US$ 136	ND	Total cost (cost in performing the strategy + expected outcome cost): US$ 23 (no intervention); US$ 272 (vaccination without screening) and US$ 298 (vaccination after screening). The most benefit was gained by no intervention strategy.	[35,24,25]
Valuenzela *et al.*, 2001	US$ 9.4	US$ 4.7	Healthcare perspective: US$ 241/QALY gained (vaccination at 18 and 54 months) and US$ 431/QALY gained (vaccination at 18 and 24 months). Societal perspective: cost-saving.	[28,24,25]

*Included the administration cost
ND: not determined; CLD: chronic liver disease; QALY: quality-adjusted-life-year.

In two CBAs from 2002, Soogarun *et al.* and Teppakdee *et al.* concluded that vaccination against HAV in Thailand, a low-incidence country, would not be a cost-beneficial intervention [33,35]. Comparing two scenarios (vaccination with or without screening), which focused only on the adolescent group (12-18 years old), Soogarun *et al.* confirmed that hepatitis A vaccination would not be a cost-beneficial intervention in Thailand under all scenarios [35]. Notably, no vaccination was more beneficial than vaccination with or without screening strategies [35]. Differing from a study conducted by Soogarun *et al.*, Teppakdee *et al.* conducted a CBA study in three age-groups: 3-11, 12-18 and 19-40 years old [33]. Nevertheless, the vaccination strategies were still not cost-beneficial in all of those scenarios [33]. Teppakdee *et al.* carried out sensitivity analyses and confirmed that the incidence rate and the vaccine price were the most critical parameters [33].

Valenzuela *et al.* compared three vaccination strategies in Chile: vaccination at 18 and 24 months, at 18 and 54 months, and no vaccination [28]. Compared to no vaccination, vaccination would cost US$ 431and US$ 241 per QALY gained for vaccination at 18 and 24 months and at 18 and 54 months, respectively from the healthcare perspective, while from the societal perspective it would be cost-saving for both vaccination schedules [28]. In the context of cost-effectiveness criteria, this study used a conventional consideration that an intervention would be cost-effective if the ICER does not exceed the GDP per capita [28,61]. Using the GDP per capita in 2012 of US$ 15,363, vaccination would be considered as a cost-effectiveness intervention, even without considering the work loss in the societal perspective [28]. Sensitivity analyses were carried out from the healthcare perspective. It appeared that the ICER was most sensitive to the discount rate, medical costs and vaccine price [28].

Quezada *et al.* estimated that a two-dose vaccination (12 and 18 months) program for toddlers in Chile would save US$ 3,625 per QALY gained [29]. This study analyzed that the total costs (direct costs, indirect costs and vaccination costs) would increase temporarily for 5 years; and both direct and indirect costs would decrease thereafter [29]. This would make vaccination a cost-saving program after 6 years and within 8 years, even if indirect costs were not considered [29]. Sensitivity analyses confirmed that vaccination coverage, time horizon, annual decrease on force of infection, discount rate, herd immunity and disease costs were the most influential parameters. Applying the best-case assumptions, vaccination would annually save US$ 13,575,133 and 3,745 life years for the cohort of toddlers of 12 to 18 months [29]. Additionally, the break-even price per dose of hepatitis A vaccine in the base case was US$ 35 from the societal perspective [29].

In Ellis *et al.*, three vaccination strategies were compared to no vaccination: vaccination at (i) 12 months, (ii) 12 and 18 months, and (iii) 12 and 72 months [30]. The study was

conducted in five regions in Argentina: Northeast, Central, South, Cuyo and Northwest [30]. The study showed that the ICERs would be at cost-saving, US$ 401 and US$ 690 per QALY gained for vaccination at 12 months, at 12 and 18 months, and at 12 and 72 months, respectively, in Argentina [30]. Comparing the different levels of endemicity, the ICERs would be at cost-saving, US$ 489 and US$ 2,016 per QALY gained in Cuyo (high endemicity), South (intermediate endemicity) and Northeast (low endemicity), respectively, when the vaccination at 12 and 18 months was implemented [30]. Ellis *et al.* used a threshold for cost-effectiveness expressing that medical interventions are conventionally considered a cost-effective strategy if the ICER does not exceed the GDP per capita [30,61]. Considering the GDP per capita in 2012 of US$ 11,558, vaccination would be accepted as a cost-effective intervention in all regions in Argentina. An increase of 10% and 20% of vaccine prices with protection waning at half and twice the rate in base-case, vaccination remained a cost-effective intervention [30]. Notably, the implementation of single-dose hepatitis vaccination was the most cost-effective intervention in this study.

Implementing the two-doses vaccination program at 12 and 18 months in Argentina, Lopez *et al.* estimated that vaccination would save US$ 2,838 per QALY gained [31]. It would substantially reduce the direct and indirect costs within 10, 20 and 50 years of time [31]. The treatment costs, discount rate, level of herd immunity, and decreasing rate on force of infection were varied in sensitivity analyses [31]. Cost savings remained in these alternative calculations. In particular, the break-even cost per dose of hepatitis A vaccine in the base-case was US$ 21 [31], which was four times higher than the current vaccine price of US$ 5.

Zhuang *et al.* compared the cost-effectiveness of vaccination (at 12 and 18 months) to no vaccination in five regions based on anti-HAV prevalence: the lowest, lower, intermediate, higher and the highest infectious region, covering 31 provinces of Mainland China [32]. Vaccination would be cost-saving in the lowest, lower, intermediate, higher and highest infectious regions from both the healthcare and the societal perspectives [32]. Yet, in the highest infectious region vaccination would require additional costs at US$ 149 and US$ 201 per QALY gained from the healthcare and the societal perspectives, respectively [32]. In sensitivity analyses, varying several parameters within the plausible ranges still indicated vaccination cost-saving in all regions [32].

The study in Egypt was the only one study focusing on a specific, targeted group, *i.e.,* children with CLD [34]. Considering the test cost for anti-HAV at US$ 6 per test and the vaccine price per dose at US$ 15, the study concluded that children with CLD>2 years old are recommended to be vaccinated to prevent serious complications from superimposed liver insult on their diseased livers at acceptable cost-effectiveness [34]. It confirmed the result

from a previous study in the United States that hepatitis A vaccination in people with CLD was recommended [67]. Additionally, it showed that pre-screening in the group of children with CLD >5 years old would be cheaper than in the group of children with CLD <5 years old [34].

Discussion

Our systematic review suggests that universal hepatitis A vaccination of infants, children and adolescents in MICs is cost-effective in the intermediate-endemic countries (Argentina, Brazil, Chile, China and Egypt, were investigated in detail). In those countries, universal vaccination is economically attractive since people are mostly infected during the childhood, the disease is asymptomatic and a large proportion of the adult population is relatively susceptible to HAV. In contrast, for a low-endemic country (Thailand), as infection might occur only among specific risk groups (such as travelers), a large-scale vaccination program is unlikely to be cost-effective. Incidence is one of the major factors, which determine the cost-effectiveness results. In particular, two studies in Thailand confirmed that immunization against HAV was not cost-beneficial since HAV infections might lead to outbreaks only occasionally [33,35]. For targeted vaccination, economic attractiveness is obviously more likely to be influenced by the level of risk in the target group and less dependent on the full population (except if investigated as an intervention to reduce the spread of infections in dynamic models) [18]. The majority of the studies confirmed that vaccine price, medical costs, incidence and discount rate were the most influential parameters in the sensitivity analyses. A change in these parameters would give a significant effect on the ICERs in both societal and healthcare perspectives. Notably, these findings are congruent with other economic studies of hepatitis A vaccination [18,20,41].

Most of the studies on economic evaluations of hepatitis A immunization in MICs confirmed that hepatitis A immunization is cost-effective or even cost-saving under certain conditions. It has been shown that for MICs, it is very essential to make an appropriate design and infrastructure related to the HAV vaccine delivery and acquisition policies in order to implement hepatitis A vaccination effectively, since MICs are unlikely to receive financial assistance on vaccination program as much as LICs. Before its widespread introduction, many factors should still be considered regarding HAV vaccination. Firstly, the disease burden related to HAV is an essential factor in the priority determination for new and under-used vaccines to be introduced into the national immunization programs (NIP), especially for policy makers in MICs with limited immunization budget and financial assistance. In a MIC with a relatively higher level of endemicity, it would be more urgent to

introduce universal hepatitis A vaccination. Secondly, cost-effectiveness should be applied to determine the price at which hepatitis A vaccination should be introduced into the NIP. Most of the studies in this study confirmed that vaccine price is the most important factor influencing the cost-effectiveness results. Finally, health system characteristics (immunization schedule, vaccine security, possibility of local vaccine and cost) present critical factors whether the proposed intervention can be accepted in a MIC [68]. Potentially, introducing a new vaccine into the NIP would require a new infrastructure in the healthcare system of the considered MIC [69].

In conclusion, the ICERs from various studies are useful to summarize the cost-effectiveness of hepatitis A vaccination programs. Several limitations were found in the review. Applying a static model instead of using a dynamic model tends to underestimate the cost-effectiveness result. The majority of the studies applied static models or straightforward calculations without a formal model design, and only three studies applied dynamic models. Due to the ability to incorporate the epidemiology of hepatitis A and the development of herd immunity, dynamic models are generally preferred in the cost-effectiveness analysis for vaccination strategies. For applying static models, an exception might occur when the vaccine coverage is almost 100% and herd immunity might validly be excluded. However, implementation of 100% vaccine coverage is unlikely for vaccination strategies in MIC. Most of the studies did not apply a dynamic model in this review, possibly because it required larger amounts of data, which were not available in these MICs, and as static models indicate favorable cost-effectiveness, results from dynamic models would be cost-effective.

Applying the discount rate for costs and health effects at the same rate is another methodological issue highlighted in this review. Despite the majority of the recent studies applying the same discount rate for health effects and costs at 3%-5%, the practice is debatable. Previously, it was conservatively argued by health economists that costs and health effects should be discounted at the same rate [70,71]. Weinstein *et al.* argued that the opportunity of individuals to transform income into health could only happen if costs and health effects were discounted at the same rate [72]. On the other hand, Gravelle *et al.* argued that health effects should be discounted at a lower rate if health effects are measured in quantities (*e.g.,* QALYs) because the value of health effects increases over time [70]. Also, WHO recommended that costs and health effects should be discounted at the same rate, yet considering a lower discount rate of health effects in the sensitivity analyses [73]. Notably, it is highly worthwhile to consider a lower discount rate for health effects in sensitivity analyses since this may heavily impact results [73]. Such differential discounting would help policy makers in implementing health interventions more appropriately related to the

relative valuation of future life and QALYs. Notably, only five studies in this review applied a lower discount rate for health effects in the sensitivity analyses [27-29,31,32].

Another limitation concerns the productivity loss data related to caregivers. Only two studies considered the productivity loss for caregivers. Brouwer *et al.* argued that the effects of treatments on family members should be included in economic evaluations [74]. Economic evaluations are designed to inform policy maker about the most appropriate healthcare intervention. As recommended in such evaluations [74,75], applying the societal perspective takes all relevant costs and effects into account. Absence of productivity (or even QALY) losses related to caregivers might yield non-optimal decisions considering overall welfare [76].

A further limitation is associated with the lack of data. In the absence of data on the age-specific proportions of icteric cases, most of studies used US data associated with the epidemiological estimates. Also, four studies applied the US data related to case-fatality, in the absence of local data. Additionally, applying the dynamic model designs in their studies, Quezada *et al.* and Lopez *et al.* made an assumption that the force of infection would decrease at an annual rate of 1% in the base case, again in the absence of actual local data. However, the authors varied their estimates extensively in multiple sensitivity analysis in their studies to overcome those limitations. Regarding the resource limitations in MICs, implementation of single-dose vaccination could be considered and the schedule of hepatitis A vaccination should be chosen based on the schedule of other vaccines, which are already incorporated into the NIP [30].

Obviously, vaccine price has been shown as a strong barrier for MICs in implementing universal vaccination of hepatitis A since MICs are unlikely to receive health budgets as HICs do and financial aids from international organizations as LICs do. Despite all studies in this review confirmed that the implementation of hepatitis A vaccination at the base-case would be a cost-effective intervention, saving funds could enhance the implementation of other vaccination programs in MICs. Thus, the most feasible solution to overcome this problem is through negotiations with the vaccine manufacturing companies to achieve discount prices and using the existing infrastructure for the introduction of new vaccines, such as existing self-sustaining storage, to minimize the required budget. Additionally, using the combined hepatitis A/B vaccine instead of monovalent vaccines could be considered to reduce the administration costs and it might be a solution to produce more favorable cost-effectiveness ratios. Indeed, the combined hepatitis A/B vaccine has proved to be a highly immunogenic and well-tolerated vaccine [77] and in many studies it has been confirmed as a more cost-effective intervention compared to the monovalent vaccines [78-80].

From this review, it can be concluded that hepatitis A immunization in MICs is generally cost-effective both from the healthcare and societal perspectives, due to savings of the future treatment cost from HAV infection, especially in the intermediate and high endemic countries. The result confirms that immunization is cost-effective next to an effective way to prevent HAV infection. Yet, further high-quality economic evaluations in MICs are still required in the near future. Hopefully, the results of this study could help national and international policy makers in making effective decisions related to the implementation of hepatitis A immunization programs in MICs.

Expert commentary

As countries with a mixture of intermediate and low endemic levels, MICs might experience an increased clinical incidence and fatal cases due to the high risk on transferring HAV infection from high-endemic (LICs) into intermediate-endemic (MICs). In this case, universal hepatitis A immunization is likely to be even more cost-effective in most of MICs. To control community-wide outbreaks, a single dose of hepatitis A vaccine has been proven an effective strategy if vaccination was started early and applied with high coverage. Compared to the two-dose schedule, single doses of vaccine are less expensive and easier to implement. However, in high-risk groups (such as children with CLD and immune-compromised individuals) for hepatitis A, a two-dose schedule is preferred. In MICs with low endemicity, targeted vaccination of high-risk groups should be considered although the hepatitis A vaccine in high-risk groups has been associated with lower efficacy and shorter durations of protection, compared to vaccinating a healthy young population. Additionally, vaccination against HAV infection should be part of a comprehensive plan related to both prevention and control of HAV. It should be integrated into the NIP schedule for children ≥1 year based on age-specific epidemiological and cost-effectiveness considerations. The decision to implement HAV immunization programs in MICs is definitely influenced by two major factors: the incidence of acute HAV infection and the vaccine price.

Five-year view

Due to its generally attractive characteristics on financial capability, high-quality economic evaluations of HAV immunization in MICs have to be conducted in different settings in the next 5 years to support rational implementation in these settings. For instance, the cost-effectiveness of the combined hepatitis A/B immunization has to be urgently evaluated, especially as a solution to reduce the administration costs and so yielding more cost-effective

intervention. Although, the price of the combined hepatitis A/B vaccine is higher compared to the prices of the monovalent vaccines, the initial higher cost would be covered in the future by its capabilities on generating savings on the direct and indirect costs of HAV and HBV. Furthermore, the decision makers in MICs have to design the best strategy to spend health budgets effectively with a main barrier of limited financial assistance from international organizations for those MICs. Collaboration with research communities, both national and international, is required to conduct an ideal intervention/implementation of HAV immunization in MICs.

Key issues

- Approaches to conduct economic evaluations of hepatitis A vaccination in MICs varied widely and we found that several studies did not completely fulfill the criteria on quality assessment.
- We found evidence that universal hepatitis A vaccination of infants, children and adolescents in MICs has favorable cost-effectiveness in high- and intermediate-endemic countries and potentially unfavorable in low-endemic countries.
- Vaccine price, medical costs for HAV, incidence and discount rates were found as the most influential parameters in the sensitivity analyses.
- Implementation of a single-dose hepatitis A vaccine has been proven to potentially be a cost-saving intervention in one of MICs.

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CHAPTER 7

Cost-effectiveness of hepatitis A vaccination in Indonesia

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Abstract

Objective

This study aims to assess the cost-effectiveness of hepatitis A vaccination in Indonesia, including an explicit comparison between one-dose and two-dose vaccines.

Methods

An age-structured cohort model based on a decision tree was developed for the 2012 Indonesia birth cohort. Using the model, we made a comparison on the use of two-dose and one-dose vaccines. The model involves a 70-year time horizon with 1-month cycles for children less than 2 years old and annually thereafter. Monte Carlo simulations were used to examine the economic acceptability and affordability of the hepatitis A vaccination.

Results

Vaccination would save US$ 3,795,148 and US$ 2,892,920 from the societal perspective, for the two-dose and one-dose vaccine schedules, respectively. It also would save 8,917 and 6,614 discounted quality-adjusted-life-years (QALYs) for both schedules. With the vaccine price of US$ 3.21 per dose, the implementation of the hepatitis A vaccine from the societal perspective would yield incremental cost-effectiveness ratios (ICERs) at US$ 7,421 and US$ 4,933 per QALY gained for the two-dose and one-dose vaccine schedules, respectively. Considering the 2012 gross-domestic-product (GDP) per capita in Indonesia of US$ 3,557, the results indicate that hepatitis A vaccination would be a cost-effective intervention, both for the two-dose and one-dose vaccine schedules. Vaccination would be 100% affordable at budgets of US$ 71,408,000 and US$ 37,690,000 for the implementation of the two-dose and one-dose vaccine schedules, respectively.

Conclusions

The implementation of hepatitis A vaccination in Indonesia would be a cost-effective health intervention under the market vaccine prices. Given the budget limitations, the use of a one-dose vaccine schedule would be more realistic to be applied than a two-dose schedule. The vaccine price, mortality rate and discount rate were the most influential parameters impacting the ICERs.

Introduction

Approximately 1.4 million cases of hepatitis A virus (HAV) infection occur annually worldwide and almost half of those cases are reported in Asia [1]. HAV is primarily transmitted from person to person by the fecal-oral route and the ingestion of contaminated foods or drinks [2]. As the World Gastroenterology Organization (WGO) reported that poor hygiene and poor sanitation pose the greatest risk related to HAV infection [3], the incidence rate of HAV infection in a country is inversely related to its wealth [2]. In Asia, the endemicity levels of HAV infection vary considerably between countries [4]. Several countries still have a high endemicity level (*e.g.,* India, Bangladesh and Pakistan), other countries are intermediate in level (*e.g.,* Uzbekistan, Kazakhstan and Azerbaijan) or low (*e.g.,* Indonesia, China and Thailand) [5]. In particular, three high-income countries in Asia (Japan, South Korea and Singapore) are classified into the very low endemicity level [5].

Despite the relatively low endemicity of HAV infection in Indonesia, a substantial proportion of adolescents and adults may be susceptible to infection due to social developments, such as globalization, migration and travel patterns [6]. Additionally, as a middle-income country with continuously improving sanitation, it has been reported that fewer children in Indonesia are infected by HAV in early childhood than earlier [7]. Yet, this condition paradoxically may lead to a higher disease incidence, since HAV disease primarily manifests itself in older age groups. In the context of hepatitis A prevention, it has been emphasized that the most effective way is through vaccination, which has been implemented in several countries and has reduced hepatitis A cases significantly [8]. In Indonesia, where transmission occurs primarily from person to person in the general community and hepatitis A outbreaks periodically happen, control of hepatitis A also may be achieved through a widespread vaccination program.

Until now, an economic evaluation on hepatitis A vaccination has not yet been conducted in Indonesia. It is important to know whether potential favorable cost-effectiveness may exist within the context of the Indonesian government perspective to justify full inclusion of the hepatitis A vaccine into the national immunization program (NIP). The objective of this study is to assess the cost-effectiveness of hepatitis A vaccination in Indonesia, including an explicit comparison between one-dose and two-dose vaccine schedules.

Methods

Model

In this study, we applied a birth cohort of 4,200,000 infants [9] in an age-structured cohort model based on a decision tree. The model involves a 70-year time horizon (the average life expectancy in Indonesia) [10] with 1-month cycles for children less than 2 years old and annually thereafter. Differing from several previous studies in Asia [11-13], we made a comparison on the use of a two-dose versus a one-dose vaccine schedule. The model was run in Microsoft Excel 2010 and @Risk 4.5.4 was used in probabilistic sensitivity analysis (see Figure 1).

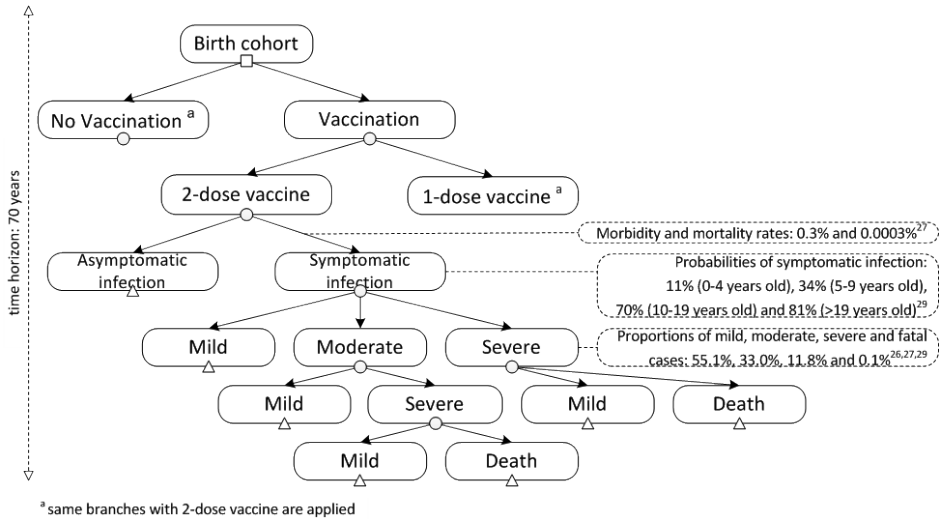

Fig. 1. Decision analytic model

Incidence of HAV infection

We classified HAV infection into four levels of severity which are generally used for global assessments: mild (home treatment), moderate (general practitioner treatment), severe (hospitalization) and fatal cases [14]. From the World Bank's report in 2006 on economic impacts of sanitation in Indonesia [15] and considering the annual incidence of HAV infection declining linearly at an average annual rate of 2% as the result of socioeconomic improvement [11], we obtained the number of hepatitis A cases in 2012 (mild, moderate, severe and fatal cases) by considering the morbidity and mortality rates of 0.3211% and 0.0003% [15]. We estimated the total number of severe cases by applying the ratio of hospitalization (severe) and outpatient visit (mild-moderate) at 11.8%:88.2% according to a study by Zhuang *et al.* [11]. For the number of severe cases in each age group, we applied

data from a study on hepatitis A cases at one of biggest public hospitals in Indonesia during 2011 [16]. Furthermore, we estimated that moderate cases would make up 37.5% and mild cases 62.5% from outpatient visit cases based on a study by Buma *et al.* [14]. Several data from previous studies related to the age-specific probabilities of symptomatic infection [17], hospitalization rate [16] and case fatality rate [11] were used to estimate mild-moderate, severe and fatal cases in various age groups. For economic consequences, we only consider symptomatic infections since asymptomatic infections were assigned no costs and excluded from further follow-up for disease outcomes [11]. As the liver transplant in acute hepatitis patients with fulminant liver failure is very rare in Indonesia, we did not take this into account (see Figure 2).

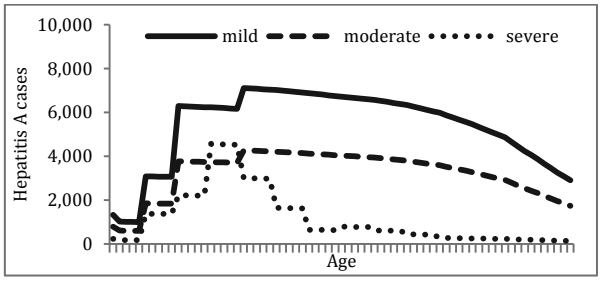

Fig. 2. Age-specific hepatis A-associated case

Vaccine characteristics

Hepatitis A vaccine would be given in a two-dose schedule at 12 and 18 months of age and in a one-dose schedule at 12 months of age. We applied vaccine efficacy at 93% and 95 % for the first and second dose, based on vaccine immunogenicity and safety studies [18-20]. Furthermore, we assumed that with the two-dose vaccine schedule, vaccine protection would annually decline by 0.31% within the first 10 years and 0.62% thereafter according to the expert panel opinion [21]. In the one-dose vaccine schedule, vaccine protection would annually decline by 1.62% within the first 10 years and 2.67% thereafter [21]. Vaccine coverage in this study was assumed to be 80% for both the two-dose and one-dose vaccine schedules, according to a previous hepatitis B study conducted in Indonesia (see Table 1) [22].

QALY (quality-adjusted-life-year) losses

To estimate QALY losses, we applied data from several previous studies with estimated durations of illness at 16, 21 and 33 days for mild, moderate and severe cases, respectively [10], and disutility scores at 0.43 for the state lived with hepatitis A [23]. Based on those

data, we estimated QALY losses, *e.g.,* mild cases at 0.01885 (16 x 0.43 / 365 days) [24]. We applied the same method for estimating QALY losses for moderate and severe cases. We did not consider caregiver QALY losses in our study (see Table 1).

Table 1
Parameters used in the model

Parameters	Baseline	Distribution	References
Vaccine coverage	80%	Normal (95%CI; 76.64-83.36%)	[37]
Vaccine efficacy			
1st dose	93%	Normal (95%CI; 89.10-96.90%)	[13]
2nd dose	95%	Normal (95%CI; 91.01-98.99%)	
Annual loss of vaccine protection			
1-dose schedule (1-10 years)	1.62%	NA	[36]
1-dose schedule (> 10 years)	2.67%		
2-dose schedule (1-10 years)	0.31%		
2-dose schedule (> 10 years)	0.62%		
Probability of symptomatic infection			
0-4	11%	NA	[31]
5-9	34%		
10-19	70%		
20+	81%		
Hepatitis A hospitalization rate			
0-4	1.05%	NA	[32]
5-9	8.42%		
10-14	13.68%		
15-19	28.42%		
20-24	18.95%		
25-29	10.53%		
30-34	4.21%		
35-39	5.26%		
40-44	4.21%		
45-49	3.16%		
50+	2.11%		
Hepatitis A case fatality rate			
1-14	0.030%	NA	[13]
15-39	0.054%		
40+	0.436%		
Hepatitis A cases			
Mild	381,347	Normal (95%CI; 380,137-382,556)	[13,29-32];
Moderate	228,808	Normal (95%CI; 227,871-229,745)	calculated
Severe	81,590	Normal (95%CI; 81,030-82,150)	
Death	679	Normal (95%CI; 628-730)	
Age-dependent hepatitis A related proportion of mild, moderate, severe and fatal cases		Dirichlet	[13,29-32]; calculated
Utility losses			
Mild	0.01885	Triangular	[13,29,38];
Moderate	0.02474	(using 25% lower and upper)	calculated
Severe	0.03888		
Death	1.00000		
Total healthcare costs per case (US$)			
Mild	8.77	Gamma (5.06-15.81)	[30,39];
Moderate	17.53	Gamma (25.20-55.80)	calculated
Severe	25.82	Gamma (59.50-114.30)	
Total societal costs per case (US$)			
Mild	11.31	Gamma (9.24-25.03)	[27,33];
Moderate	20.08	Gamma (34.10-71.60)	calculated
Severe	36.24	Gamma (124.50-215.80)	
Vaccination cost (US$)			
Vaccine price (per dose)	3.21	Triangular	[37,39]
Administration cost (per dose)	0.36	(using 25% lower and upper)	[9,39]
Discount rate	3%	0-5%	[13]

NA: not applicable

Hepatitis A costs

Differing from two previous studies in South East Asia Region (SEAR) [12,25], the analysis in this study was viewed from two perspectives: healthcare and societal. We only considered direct medical cost in the healthcare perspective, while in the societal perspective, we considered both direct and indirect costs. We derived our cost estimations from a 2006 study on estimated unit costs related to HAV infection due to poor sanitation in Indonesia [15]. Healthcare costs due to HAV infection related mild, moderate and severe cases were estimated from informal outpatient care (home treatment), formal outpatient care (general practitioner treatment) and formal inpatient care (hospitalization) sources, respectively [15]. For societal costs, we additionally took direct non-medical costs (*e.g.,* transportation) and indirect costs (*e.g.,* productivity loss) into account [9]. Vaccine price and administration cost per dose were applied at US$ 3.21 [22] and US$ 0.36 [9], respectively, based on previous studies in Indonesia. All results from the analyses were converted to 2012 US$ by using purchasing power parities (PPPs) [26] and all costs were discounted with a yearly rate of 3% (see Table 1).

Analytic methods

$$\text{ICER} = \frac{\text{Total cost of with vaccination} - \text{Total cost of without vaccination}}{\text{Total QALY gained without vaccination} - \text{Total QALY gained with vaccination}}$$

The incremental cost-effectiveness ratio (ICER) was calculated to measure the outcomes from both perspectives in relation to the World Health Organization's (WHO's) definition on cost-effectiveness of universal vaccinations according to the gross-domestic-product (GDP) per capita: (i) highly cost-effective (less than one GDP per capita); (ii) cost-effective (between 1 and 3 times GDP per capita); and (iii) cost-ineffective (more than 3 times GDP per capita) [27]. We performed both univariate and probabilistic sensitivity analyses (PSA). Univariate sensitivity analyses were performed to investigate the effects of different input parameters primarily by varying each parameter with ± 25% while keeping other parameters constant. PSA were performed by running 5,000 Monte Carlo simulations. The results of the PSA were presented in CEACs by using two thresholds: 2 times GDP per capita and 3 times GDP per capita. We evaluated affordability of vaccinations related to the required budget (vaccination and treatment costs) from the healthcare perspective, based on the distribution of incremental costs and health gains from the same 5,000 Monte Carlo simulations.

Results

Baseline analyses

Assuming a vaccine coverage of 80% and vaccine efficacies of 93% (first dose) and 95% (second dose), vaccination of 4,200,000 infants [9] would reduce HAV infection by 452,834 and 322,207 cases when using two-dose and one-dose vaccine schedules, respectively. In particular, the two-dose vaccine schedule would reduce hepatitis A cases by 247,694 (65.0%), 148,670 (65.0%), 56,064 (68.7%) and 406 (59.8%) for mild, moderate, severe and fatal cases, respectively. The one-dose vaccine schedule would reduce hepatitis A cases by 174,157 (45.7%), 104,579 (45.7%), 43,224 (53.0%) and 247 (36.3%) for mild, moderate, severe and fatal cases, respectively. Hepatitis A vaccination would save 8,917 and 6,614 discounted QALYs for the two-dose and one-dose vaccine schedules, respectively. Furthermore, it also would save US$ 3,795,148 and US$ 2,892,920 from the societal perspective for both schedules, respectively (see Table 2.a). The cost-effectiveness values from all perspectives are shown in Table 2.b. With a vaccine price of US$ 3.21 per dose, the implementation of hepatitis A vaccine from the healthcare perspective would yield ICERs at US$ 7,510 and US$ 5,025 per QALY gained for the two-dose and one-dose vaccine schedules, respectively. From the societal perspective, it would yield ICERs at US$ 7,421 and US$ 4,933 per QALY gained for both schedules. Considering the 2012 GDP per capita in Indonesia of US$ 3,557 [28], the results confirmed that hepatitis A vaccination using the two-dose and one-dose vaccine schedules would be cost-effective interventions since the ICERs were between 1 and 3 times GDP per capita [27]. Additionally, the ICERs of the two-dose over the one-dose schedule were US$ 14,648 and US$ 14,568 per QALY gained from the healthcare and societal perspectives, respectively.

Table 2.a
Results from all vaccination strategies

Vaccine	Without Vaccination	With Vaccination	Difference
Two-dose vaccine schedule			
Number of cases [a]	692,424	239,590	452,834
Mild	381,347	133,653	247,694
Moderate	228,808	80,138	148,670
Severe	81,590	25,526	56,064
Death	679	273	406
Cost of illness			
Healthcare perspective [b,c]	$ 4,441,405	$ 1,437,763	$ 3,003,642
Societal perspective [b,c]	$ 5,604,793	$ 1,809,645	$ 3,795,148
Cost of vaccination program			
Acquisition cost [b]	0	$ 62,859,401	($ 62,859,401)
Administration cost [b]	0	$ 7,107,260	($ 7,107,260)
Total vaccination cost [b]	0	$ 69,966,661	($ 69,966,661)
QALYs lost [b]	13,896	4,980	8,917
One-dose vaccine schedule			
Number of cases [a]	692,424	370,217	322,207
Mild	381,347	207,190	174,157
Moderate	228,808	124,229	104,579
Severe	81,590	38,366	43,224
Death	679	432	247
Cost of illness			
Healthcare perspective [b,c]	$ 4,441,405	$ 2,155,823	$ 2,285,582
Societal perspective [b,c]	$ 5,604,793	$ 2,711,873	$ 2,892,920
Cost of vaccination program			
Acquisition cost [b]	0	$ 31,914,096	($ 31,914,096)
Administration cost [b]	0	$ 3,608,398	($ 3,608,398)
Total vaccination cost [b]	0	$ 35,522,494	($ 35,522,494)
QALYs lost [b]	13,896	7,348	6,859

[a] Undiscounted
[b] Discounted
[c] Costs are excluding vaccination cost

Table 2.b
Cost effectiveness results

Cost effectiveness of vaccination	One-dose	Two-dose
Vs no vaccination		
Net cost per QALY gained (healthcare) [a]	US$ 5,025	US$ 7,510
Net cost per QALY gained (societal) [a]	US$ 4,933	US$ 7,421
Vs one-dose vaccine schedule		
Net cost per QALY gained (healthcare) [a]		US$ 14,648
Net cost per QALY gained (societal) [a]		US$ 14,568

[a] Discounted

Univariate, probabilistic sensitivity and affordability analyses

The effects of varying input parameters on the ICERs are shown in a tornado chart (see Figure 3). For the schedule using two administrations, the result confirmed that the vaccine price, mortality rate and discount rate provide most impact on the ICERs. The cost-effectiveness acceptability curves (CEACs) from the societal perspective showed that at the

threshold ICER of US$ 7,114 (2 times GDP per capita), the probability for the implementation of hepatitis A vaccination to be cost-effective would be 38.18% and 100% for two-dose and one-dose vaccine schedules, respectively. If a threshold ICER of US$ 10,671 (3 times GDP per capita) were used, the probability for the implementation of hepatitis A vaccination to be cost-effective would be 100% for both vaccine schedules (see Figure 4.a). The affordability curves related to the required budget for vaccination from the healthcare perspective, are shown in Figure 4.b. At budgets of US$ 71,408,000 and US$ 37,690,000 for the implementation of the two-dose and one-dose vaccine schedules, the implementation of hepatitis A vaccination would be 100% affordable.

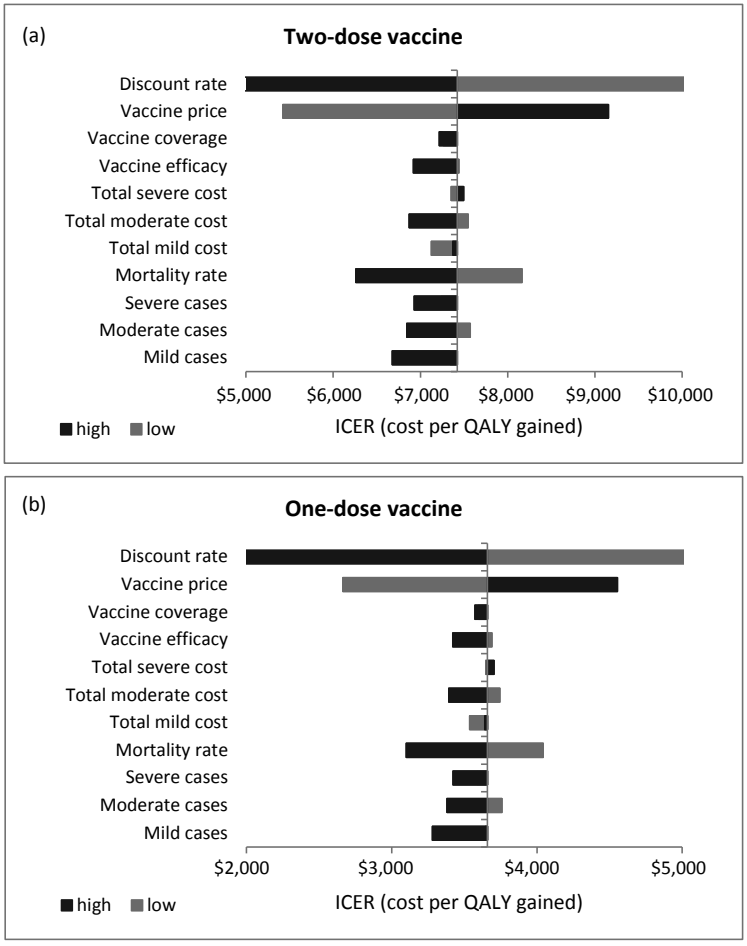

Fig. 3. Univariate sensitivity analyses from societal perspective

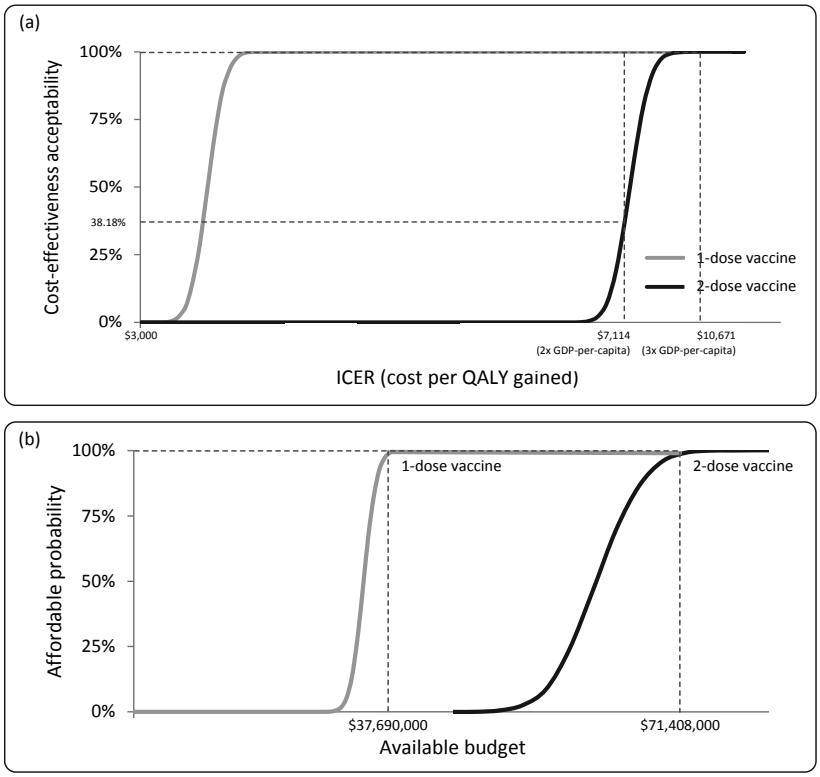

Fig. 4. (a) Cost-effectiveness acceptability curves from the societal perspective
(b) Affordability curves from the healthcare perspective

Discussion

As a consequence of the improvement in hygiene and sanitary conditions, which are coupled with the economic rising of Indonesia from a low-income country into a middle-income country, the incidence of HAV infection has gradually declined. Without vaccination, HAV causes 692,424 cases in Indonesia where the disease acquisition occurs in adulthood rather than childhood as a typical of hepatitis A case in a low endemicity country [29]. Applying a vaccine coverage at 80%, vaccination of a birth cohort of 4,200,000 would reduce HAV-cases by 452,834 and 322,207 for vaccination with the two-dose and one-dose vaccine schedules, respectively. The cost-effectiveness analyses yielded ICERs from the societal perspective at US$ 7,421 and US$ 4,933 per QALY gained for both vaccine schedules. Our finding that the implementation of universal hepatitis A immunization could be cost-effective even in a low endemicity country, such as Indonesia, is linear with a previous study [11]. It could be emphasized that incidence was only one of the major determining factors for the cost-effectiveness of universal hepatitis A vaccination. Even in very low endemic countries, such

as Canada and certain parts of the United States, universal vaccination could be a cost-effective intervention [30]. However, in other very low endemic countries, for instance in Belgium and Australia, it was shown that two-dose universal childhood hepatitis A vaccination was not cost-effective, using dynamic and static models, respectively [31,32]. These results are mainly influenced by estimated disease incidence, vaccine price, the schedule and the inclusion of societal cost [30]. In particular, another finding that the implementation of the one-dose vaccine schedule would be more cost-effective intervention compared to the two-dose vaccine schedule is in line with a previous study in Argentina [33]. This further warrants future attention on the implementation of the one-dose vaccine schedule, especially to control community-wide outbreaks since a single dose of hepatitis A vaccine has been proven an effective strategy if vaccination was started early and applied with high coverage. Additionally, compared to the two-dose vaccine schedule, the one-dose vaccine schedule is cheaper and easier to be implemented. Yet, in high-risk groups (such as children with chronic liver disease and immune-compromised individuals) for hepatitis A, a two-dose vaccine schedule is still preferred [8]. In the context of the health economic perspective, however, the implementation of the one-dose vaccine schedule would be more realistic to be implemented in Indonesia. Related to the sensitivity analyses, the results in this study reconfirmed the results from several previous studies that the vaccine price [12,34,35], mortality rate [36], and discount rate [30,34,37,38] were the most influential parameters impacting the ICERs in the implementation of hepatitis A vaccination. However, the dominant role of the vaccine price might lead the small difference between the ICERs from the healthcare and societal perspectives [25].

This study is the first economic evaluation study on hepatitis A immunization in Indonesia. Yet, we do not present the first economic analysis on that matter in SEAR. Compared to the previous studies in Thailand [12,13], our study has some significant differences in the process of analysis. Firstly, we explicitly compared the two-dose and one-dose vaccine schedules in a cost-effectiveness study in order to investigate the difference on the cost-effectiveness results by performing the ICERs of both vaccines over without vaccination, while two previous studies used only one vaccine schedule in their cost-benefit analyses. We also performed the ICERs of the two-dose over one-dose vaccine schedules. Secondly, we adopted both the healthcare and societal perspectives in our study. However, the healthcare perspective is relevant for assisting decision makers in the health sector only, while the societal perspective is often preferred to reflect the full public health impact. Thirdly, we performed an age-structured cohort model based on a decision tree by dividing the outpatient cases into two different levels: mild (requiring home treatment) and moderate

cases (requiring general practitioner treatment), and considering the annual decline of infection incidence and the annual loss of vaccine protection that would render results that are more precise and valid.

Nevertheless, several limitations were found in this study. The first and main limitation is that we use a static model rather than a dynamic model, which has the ability to incorporate the effect of herd immunity. In general, the static model tends to over-estimate the cost-effectiveness result. Notably, there would be an even more favorable cost-effectiveness if we took herd immunity into account. Next to the ability to incorporate the epidemiology of hepatitis A and the development of herd immunity, the disadvantage of a dynamic model is the requirement for data, which are currently scarce in Indonesia. Particularly, the age specific force of infection is difficult to be estimated as it requires serial seroprevalence data and social contact data. The second limitation is the lack of vaccine efficacy data for different levels of severity: mild, moderate, severe and death. Even though we applied different vaccine efficacy for the first dose and second dose, we applied the same vaccine efficacy for all levels of severity, thus the vaccine efficacy might be over or underestimated. The third limitation is the lack of specific local data related to the proportion of incidence for all levels of severity. In this study, we derived those numbers from international data. Yet, we varied these estimates extensively in multiple sensitivity analyses. Finally, we applied treatment costs from a 2006 study on estimated unit costs related to HAV infection due to poor sanitation in Indonesia and these costs were inflated to 2012 price levels. Obviously, hepatitis A vaccination would be more cost-effective when the treatment costs are higher, and *vice versa*.

Our study provides information for policy makers in Indonesia to justify full inclusion of the hepatitis A vaccine into the NIP. With the market price of US$ 3.21 per dose, vaccinating using both the two-dose and one-dose vaccine schedules could be a cost-effective intervention according to the WHO's criteria for cost-effectiveness. Furthermore, when we took uncertainties into account, the implementation of universal hepatitis A immunization would not be affordable when the budget does not exceed US$ 71,408,000 and US$ 37,690,000 for the two-dose and one-dose vaccine schedules, respectively. In fact, the Indonesian government spent approximately US$ 68 million for NIP activities in 2011 [39]. Compared to the total Indonesian government health budget for the whole mandatory immunization program (hepatitis B, BCG (bacille Calmette-Guérin), diphtheria-pertussis-tetanus, measles and polio), the required investment by the Indonesian government for universal hepatitis A vaccination would be unrealistic without external support. A solution could be to reduce the vaccine price through financial aids from international organizations.

However, saving funds could enhance implementation of further vaccination programs in a country with limited vaccination budget, such as Indonesia. In particular, the implementation of the one-dose vaccine schedule could be considered since it has been proven to be the most cost-effective intervention in this study. Using the combined hepatitis A/B vaccine instead of monovalent vaccine could be considered to reduce the administration costs since the combined hepatitis A/B vaccine has been proven as a highly immunogenic and well-tolerated in a previous study [40]. Hopefully, this study helps the Indonesian government in making regulation to reduce the incidence of HAV infection in Indonesia, in line with WHO's goal on the implementation of universal vaccination.

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CHAPTER 8

GENERAL DISCUSSIONS

Partially adapted from:
"Introducing non-traditional vaccines in Indonesia:
rotavirus and hepatitis A as reference cases"

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Submitted to Expert Review of Vaccines

Summary

Despite its steadily increasing economic level, Indonesia is still facing many challenges to introducing non-traditional vaccines. This paper proposes a framework for introducing non-traditional vaccines in Indonesia by using rotavirus and hepatitis A immunization as two reference cases. Given its relatively limited immunization budget, the implementation of non-traditional vaccines in Indonesia appears to be strongly dependent on the financial arrangement of the immunization programs. Exploration of new sources of development financing is required to ensure the sustainability of new additional programs. Identifying barriers and choosing financial plans are also fundamental aspects in the health sector, and should be fully integrated into the planning and management of the Expanded Program on Immunization (EPI) in Indonesia.

Introduction

Since the access to vaccines for children in developing countries began to expand rapidly in the mid-1970s with the establishment of the Expanded Program on Immunization, many millions of deaths and illnesses has been subsequently prevented [1]. The EPI in Indonesia, launched by the Ministry of Health in 1977, recommended that all children should receive vaccines against six major preventable childhood diseases: tuberculosis (BCG), diphtheria-pertussis-tetanus (DPT), polio and measles [2]. The hepatitis B vaccine was included in this program in 1997 [2]. Additionally, the World Health Organization (WHO) has recommended that five additional vaccines be included into routine immunization programs: haemophilus influenza type b (Hib), pneumococcal, rubella, human papilloma virus (HPV) and the rotavirus vaccines [3].

Despite the fact that immunization is one of the most cost-effective strategies in the health sector, providing global health benefits and positive externalities [4], financing immunization remains a big challenge in many countries in the world. It has been reported that many immunization programs in developing countries are financially and organizationally weak due to their high dependency on funding from external sources [5]. The sustainability of an immunization program is strongly associated with reliable funding since this is required to ensure continuity in immunization services and to improve coverage, quality and access during implementation of both traditional and non-traditional vaccines. This paper proposes a framework on introducing non-traditional vaccines in Indonesia, which is a middle-income country (MIC) with a limited immunization budget, by using rotavirus and hepatitis A immunization as two reference cases. Furthermore, identifying barriers and choosing financial plans are fundamental aspects in the health sector, and it is strongly advised that these processes be fully integrated into the EPI's planning and management in Indonesia.

Rotavirus immunization: easily planned but not easily implemented

A prospective surveillance study in 2006 reported that rotavirus infections were responsible for the majority of severe diarrhea cases in Indonesian children under 5-years-old occurring throughout the year [6]. Despite this, rotavirus vaccination in Indonesia has not yet been included into the EPI. To give an idea of the situation in other countries with similar economic levels, 19 lower-middle-income countries have already introduced rotavirus vaccination into their national immunization programs [7]. In terms of economic perspectives, two studies have confirmed that implementation of the rotavirus immunization

in Indonesia would be a highly cost-effective intervention [8,9]. Based on the market price (US$ 5 per dose) and GAVI-subsidized price (US$ 0.3 per dose) for a three-dose rotavirus vaccine (Rotateq®), a previous study estimated that the Indonesian government would require a budget of US$ 65 million (market price) or US$ 10 million (GAVI-subsidized price) to implement rotavirus immunization [9]. Furthermore, another research study, which took the effect of promoting breastfeeding into account, confirmed that the Indonesian government would require a budget of approximately US$ 64 million to carry out two combined interventions: breastfeeding education and support interventions [10]. Comparing the results from these studies, it can be interpreted that breastfeeding promotion has the potential to reduce the treatment costs of rotavirus immunization in Indonesia due to its effect of decreasing rotavirus-diarrhea cases; however, breastfeeding promotion intervention can also potentially result in fewer opportunities to offset the costs of vaccination [10].

It is important that the Indonesian government introduces the rotavirus vaccination soon. Despite the urgency, the introduction may have to be delayed because further comprehensive planning and collaboration among the stakeholders involved are still needed to ensure the transition from policy to real implementation. It has been argued that incorporating new vaccines (*e.g.,* rotavirus vaccine) into traditional immunization programs in developing countries is a commitment easily planned but not easily implemented (see Table 1) [11].

Hepatitis A in Indonesia: paradox and potential

Hepatitis A is an acute illness caused by a non-enveloped virus with positive-stranded ribonucleic acid (RNA) classified into the hepatovirus genus of picomavirus family [12,13], which can be transmitted from person to person, primarily by the fecal-oral route and the ingestion of contaminated food or drink [14]. It is characterized by jaundice, dark urine, fever, anorexia, and abdominal discomfort; the symptoms are age dependent [15]. Severe complications due to the hepatitis A virus (HAV) are rare; however, the risk of death increases with age and the percentage of fatal cases may range from 0% in children under 5 years to 1.5% in people over 60 years old [15]. The paradox of hepatitis A in Indonesia is that, despite low levels of endemicity, hepatitis A outbreaks in Indonesia are very evident. Additionally, as a growing economic country with continuously improving sanitation, fewer children in Indonesia have been reported to be infected by HAV in early childhood than in earlier years [16]. This condition may also paradoxically lead to higher disease incidence, since HAV disease primarily manifests in older age groups. This paradoxical situation also

gives rise to potential opportunity regarding implementation of vaccination because, when a country improves its socioeconomic conditions, hepatitis A becomes more visible and controlling the disease through vaccination becomes more likely [15].

Using a similar method as used with the rotavirus vaccine (see Figure 1), we developed an age-structured cohort model, which involved a 70-year-time-horizon (the average life expectancy in Indonesia), to perform an analysis of cost-effectiveness and estimate the required budget for hepatitis A immunization in Indonesia [17-25]. Comparing use of the two-dose (12 and 18 months of age) and one-dose (12 months of age) vaccine schedules, we concluded that the implementation of universal hepatitis A immunization in Indonesia using either vaccine schedule would be a cost-effective intervention since costs per quality-adjusted-life-year (QALY) were US$ 7,421 and US$ 4,933 for the two-dose and one-dose vaccine schedules, respectively, which are still under 3 times the GDP per capita of Indonesia in 2012 (US$ 3,557) [26]. Additionally, the Indonesian government would require budgets of approximately US$ 90 million and US$ 47 million to implement the two-dose and one-dose vaccine schedules, respectively, of hepatitis A immunization. Obviously, it would be more realistic to apply a one-dose-vaccine schedule than a two-dose schedule in Indonesia (see Table 1).

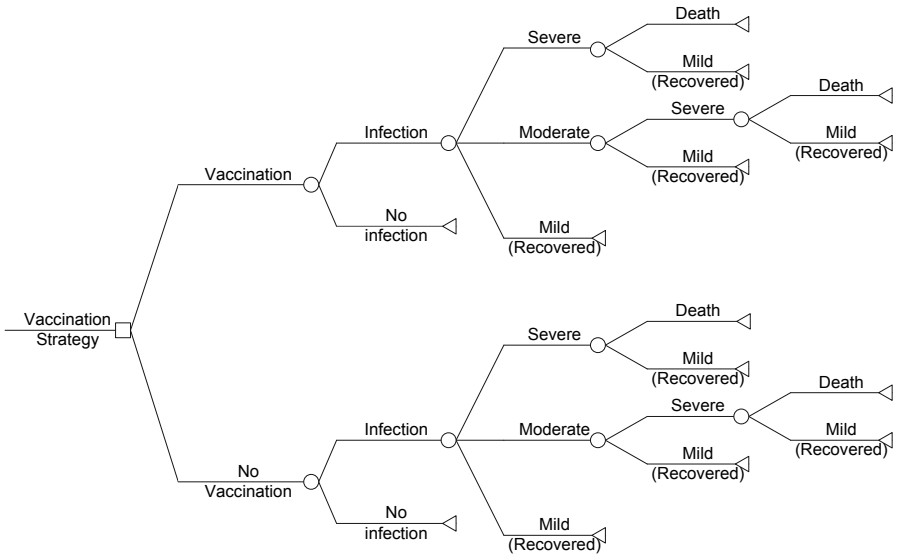

Figure 1. General decision-analytic-model for rotavirus and hepatitis A immunization in Indonesia

Table 1.
Results from rotavirus and hepatitis A vaccination in Indonesia (2012 US$)

Immunization	Primary results [a]	Required budget [b]
Rotavirus vaccine		
Market-price	Highly cost-effective	$ 51,711,482
GAVI-subsidized price	Highly cost-effective	$ 8,102,314
Hepatitis A vaccine		
Two-dose schedule	Cost-effective	$ 71,408,000
One-dose schedule	Cost-effective	$ 37,690,000

[a] According to the WHO's criteria on cost-effectiveness of immunization [26]
[b] Required budget for vaccination= vaccination costs + treatment costs (healthcare perspective)

Financial barriers to vaccines and immunization in Indonesia

Over the period 2006-2011, Indonesia's Gross Domestic Product (GDP) per capita grew from US$ 1,601 to US$ 3,472 [27], allowing Indonesia to graduate from LIC (low-income country) to MIC level. Even though its GDP per capita significantly increased, the Indonesian government's expenditure on the EPI fluctuated over this period. For example, expenditure was approximately US$ 34 million (US$ 7 per infant) in 2006 [28]. One year later in 2007, it increased to US$ 119 million (US$ 25 per infant) [28]. In 2008, it decreased again to US$ 33 million (US$ 7 per infant), which is almost the same as the total expenditure in 2006 [28]. The next year, it increased to US$ 44 million (US$ 9 per infant) [28]. In 2010, it decreased sharply to US$ 9 million (US$ 2 per infant), although it increased again to US$ 67 million (US$ 14 per infant) in 2011 [28]. Compared with the Vietnamese government's expenditure on the EPI in 2011 (US$ 7 per infant), the Indonesian government spent more on the EPI [29]. Yet, in the context of the government's general expenditure on health in 2011, the Vietnamese government spent more per infant (US$ 38) than the Indonesian government (US$ 32 per infant) [28,29]. Additionally, Vietnamese expenditure on the EPI always increased every year, and did not as fluctuate as in Indonesia. Finally, the total government contribution to immunization in Vietnam varied only between 33%-65% in 2006-2011, while it varied between 80%-100% in Indonesia over the same period (see Figure 2) [28,29].

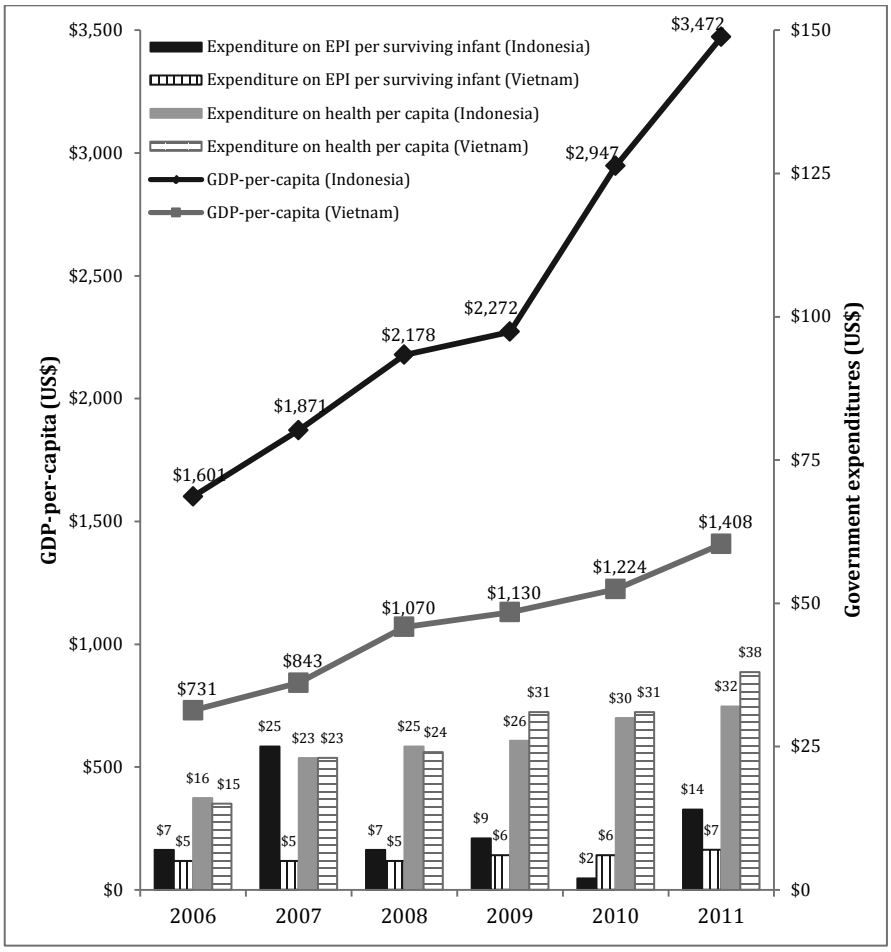

Figure 2. Government expenditures on health and EPI (Indonesia and Vietnam)

Since the EPI was launched, several targets have been reached in Indonesia. For instance, Indonesia was reported as a polio-free country in 2006, and tetanus has been eliminated from almost 90% of the Indonesian population [30]. Also, measles and rubella have been targeted for elimination by 2018 and 2020, respectively [30]. Despite these advances, the total coverage of the full immunization program is still low: only 81% as reported in 2012 [30]. This situation places Indonesia as the country with the third highest number of un-immunized children in the world. Therefore, the Ministry of Health has set a target of 100% full immunization coverage to be reached in the next few years [30]. For the Indonesian government, achieving higher levels of coverage with traditional vaccines is still the highest priority. Three other priorities are improving quality, enhancing program efficiency and

expanding the immunization schedule. Compared with LICs, Indonesia faces more complex financial barriers since MICs are unlikely to have as much access to technical and financial support of vaccination programs as LICs [31-33]. For example, despite the fact that rotavirus and hepatitis A immunization in Indonesia would be cost-effective interventions under the market prices [8,9], implementation of both immunizations would be unrealistic if the Indonesian government had to fully finance the endeavor since the required budget for both vaccinations (US$ 155 million) would be higher than the Indonesian government's total expenditure on the EPI (US$ 68 million) in 2011, which included seven traditional vaccines [28].

Financing non-traditional vaccines: lessons learned from other countries

In addition to supporting the EPI, the Indonesian government also spent another US$ 61 million on vaccines over the same period [28]. However, government expenditure on the EPI and vaccines were used only for implementing the seven traditional EPI vaccines: tuberculosis (BCG), diphtheria-pertussis-tetanus (DPT), polio, measles and hepatitis B. Given the limited budgets, implementation of non-traditional vaccines (such as rotavirus and hepatitis A) in Indonesia appears to be strongly dependent on the finance arrangement of the immunization programs. However, decisions related to these matters are usually complicated, even in high-income countries (HICs) [34]. The selection among financing options has to be made while taking into consideration the amount of required resources to achieve the EPI's goals of access, utilization, quality, safety and equity [34]. The financing arrangement also should be chosen with an understanding of the specific characteristics of each option.

Considering the relatively high cost of non-traditional vaccines, the Indonesia government should use specific strategies. In general, there are several common strategies to financing new vaccines, which can be applied from the experience of other countries. In the first strategy, governments fully finance the additional vaccines, as well as the traditional EPI vaccines [35]. The Indonesian government can apply this strategy only when vaccine prices have fallen dramatically due to a number of factors (such as competition among vaccine manufacturers). Using the introduction of the hepatitis B vaccine as a reference case, several MICs (*e.g.,* Brazil, Columbia, The Philippines and Cuba) and LICs (*e.g.,* Honduras and Zimbabwe) successfully negotiated with vaccine manufacturers to decrease vaccine price through the International Task Force on Hepatitis B Immunization. This was achieved by

convincing the manufacturers that decreasing the vaccine price would result in a potentially huge lucrative market because many new countries would be able to afford vaccines [35].

In the second strategy, donors only finance the additional vaccines [35]. This pattern has occurred in some countries in the Pacific Island region. Donor countries (*e.g.,* Australia and New Zealand) financed all of their hepatitis B vaccine supply, while the governments financed only their traditional EPI vaccines [35]. As Indonesia has graduated from LIC into MIC level, this strategy is difficult to follow in Indonesia. The most realistic way is through cooperating with vaccine manufacturers that would donate a vaccine supply for a year or two in order to create a demand for their products; thereafter, these manufacturers could charge a price for the vaccine [35]. This has been applied successfully in Costa Rica [35]. SmithKline Beecham donated 80,000 doses of Hib vaccine in 1998 to vaccinate all newborns as an initial step to create national demand for the Hib vaccine [35].

In the third strategy, governments finance the additional vaccines, while donors help fund the traditional EPI vaccines [35]. For instance, Senegal bought hepatitis B and yellow fever vaccines through government financing and received EU funding for financing the traditional vaccines [35]. Also, Kyrgyzstan bought the mumps vaccine with government funds, while receiving 100 percent financing from donors for the EPI vaccines [35]. In a similar way, the GAVI has been partially supporting the Indonesian government since 2002 for financing the EPI [36].

In the final strategy, governments charge user fees only for the additional vaccines [35]. As reported in 1996, in spite of traditional EPI vaccines being free of charge in China, patients have to pay a fee to receive some vaccines, such as the hepatitis B vaccine [35]. However, this strategy would likely create large discrepancies in coverage between urban and rural or between wealthy and non-wealthy areas, as coverage for hepatitis B was reported to be high in urban areas (90%) and considerably lower in rural areas (15-20%) [35]. In order to optimize this approach, the Indonesian government can consider applying a different fee policy to urban and rural areas, as was done in China [35].

Creating innovative mechanisms to overcome financial barriers

Since the costs of non-traditional vaccinations have increased significantly, new sources of development financing are required to ensure the sustainability of a new additional program, so that it would be financed over the medium and long term, and it would not endanger the sustainability of the government's financial position [37]. For the Indonesian government, a new fiscal space for an additional immunization could be created from efficiency gains in other health interventions, other immunization programs and from the

additional immunization program itself [37]. Expanding fiscal space also could be derived through new government financing from new revenue sources or from increased revenues, such as through economic growth, new tax administration and strengthened macroeconomic policies [37]. In this study, we evaluated several innovative mechanisms to overcome financial barriers related to the immunization programs based on experience from other countries.

Levy on airline tickets

As the first global health organization to intensify efforts in providing treatment for HIV/AIDS, tuberculosis and malaria through a tax on airline tickets, UNITAID has raised over 50% of its funds through the air ticket levy. This can vary from US$ 1 for economy-class tickets to approximately US$ 40 for business and first class travel [38,39]. The airline ticket levy can be simply added to the airport tax as long as it does not break any international regulations [39]. Potentially, the Indonesian government can apply this method to help speed up the introduction of non-traditional vaccines since Indonesia is the fastest growing emerging market in the aviation industry in Asia and, possibly, the world [40]. Indonesia's domestic market grew by 16% in 2011 to 60 million passengers, and growth is projected to continue at an annual rate approaching 20%, reaching 100 million passengers in 2015 and 180 million passengers in 2021 [40]. According to the Ministry of Transportation's data, approximately 72 million Indonesian people used airplanes for domestic (63 million people) and international (9 million people) transport in 2012 [41]. Applying an average airline ticket levy at US$ 1 for each ticket potentially would yield US$ 72 million, which could be used to contribute to immunization programs.

Simple and hassle-free donation

Another UNITAID project, which could be applied, is the voluntary solidarity contribution. The main idea is to offer individuals or corporations the possibility of making a micro donation through a simple and hassle-free process [38]. In the case of Indonesia, it also can be implemented initially in the travel and tourism industry, such as making a donation box to tick during online booking of hotel rooms, tourist attractions, and airplane and train tickets [38]. Offering a hassle-free donation option after making bank transactions at cash machines could be another alternative. For corporations, the Indonesian government could persuade them to spend their corporate-social-responsibility budgets on accelerating the implementation of non-traditional vaccines. However, these donations would have to be traceable in order to maintain accountability.

Public-private partnership in action

(RED)®, a brand created to engage business and consumer power in the fight against AIDS in Africa, can be used as an innovative example of using the marketing expertise of the public-private sector to create new resources for healthcare issues [38]. Collaborating with major corporate partners (*e.g.,* GAP®, Emporio Armani®, Apple® and Starbucks®), (RED)® has generated US$120 million since its launch in 2006 [38]. This kind of partnership could be applied in Indonesia by involving several local companies with internationally-recognized brands (*e.g.,* PeterSaysDenim®, Polygon®, Lea®, Tomkins®, The Executive® and Eiger®) to create unique branded products. Continuously growing middle- and high-class communities could be potential targets for these products through campaigns indicating that 100% of the profits made from these sales would go to help the introduction of new vaccines in Indonesia.

Levy on automotive sales

The automotive industry in Indonesia has shown robust growth in recent years. According to the Association of Indonesia Automotive Industries (GAIKINDO) and the Indonesian Motorcycles Industry Association (AISI), approximately 1.1 million cars and 7.1 million motorcycles were sold in 2012 [42,43]. Involving all automotive companies in an immunization campaign by assuming average levies of US$ 10 and US$ 1 for each car and motorcycle sold, respectively, would create additional funding of approximately US$ 18.1 million, which would provide access for a birth cohort of 4,200,000 [8,9] to non-traditional vaccines.

Discussion and policy recommendations

Sustainable, routine immunization services are strongly associated with sustainable healthcare systems in all countries throughout the world [44]. For Indonesia, there are four future challenges in the national immunization program: nationwide routine immunization, continuous disease control, non-traditional vaccines and sustainable financing (see Figure 3). In particular, financial factors play a key role in the healthcare system for ensuring sustainable funding mechanisms and maintaining the optimal usage of existing vaccines [45]. Adequate and reliable funding is one of the critical elements in ensuring the continuity of immunization programs, immunization coverage and access to both traditional and no-traditional vaccines. Generally, in the context of the Indonesian healthcare system, there are

several policy recommendations to strengthen the implementation of the EPI. The first recommendation is to apply financial and budgeting reforms. Financial and budgeting management have been proven as key strategies to increase the reliability of funding in several countries [46]. The major purposes of this strategy are: (i) to create budget lines for vaccines and immunization, and ensure greater protection of these funds within budgets; (ii) to integrate an immunization line item within expenditure frameworks; (iii) to ensure compliance with budgetary procedures; and (iv) to improve fund disbursement and cash flow management [46]. In the case of Indonesia, due to increased government expenditures in the last decade, transparency and accountability have become more important in the area of budgeting. In contrast, the Indonesian government's dependency on external partners tends to distort the budgeting process. In the context of initiating budget and financial reforms in the overall healthcare system, the best place to start is in a country's immunization program because of its complexity and domino effect on other programs [4].

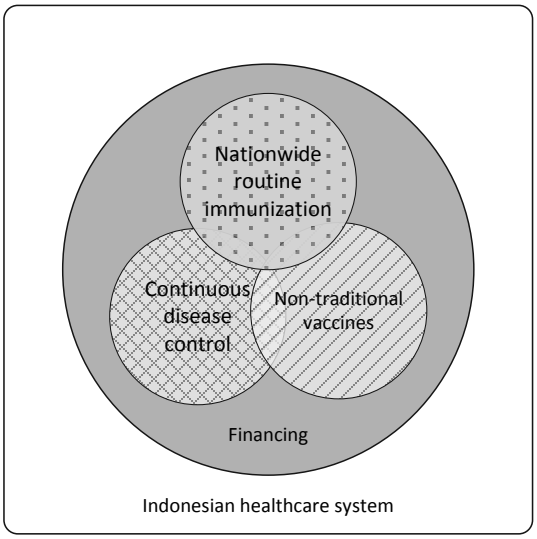

Figure 3. Future challenges in the national immunization program

The second recommendation is carrying out decentralization reforms. In Indonesia, decentralization and political reform in the late 1990s affected the sustainability of immunization funds [47]. The central government is now responsible for supplementary immunization activities, procurement of vaccines and syringes, technical assistance, development of guidelines, monitoring and evaluation, and quality control and training [47]. The district governments support the central level by taking responsibility for their

immunization programs by providing operational and handling costs [47]. However, the progress towards efficient immunization programs run by decentralized systems of government are stagnant in several countries, including Indonesia, due to the limited technical resources of the district governments and the lack of political accountability [47]. Several reform approaches applied in Kenya and Sierra Leone could be applied in Indonesia to make decentralized systems work, such as ensuring adequate access to computers and internet, and encouraging skilled workers to collaborate between government ministries [48,49].

The third recommendation is to intensify efforts on improving the efficiency of immunization. In the cases of rotavirus and hepatitis A immunization in Indonesia, there are several approaches that could be considered to improve the efficiency of immunization services. A major approach is through the implementation of combined vaccines. A previous study reported that rotavirus vaccines could be co-administered with the majority of routine childhood vaccinations [50]. In addition, a study in China reported that implementation of the one-dose rotavirus vaccine might be an alternative to the two-dose or combined vaccination [51]. For hepatitis A, using the combined hepatitis A/B vaccine instead of the monovalent vaccines could be considered to reduce administration costs [52-54]. Further research would be required to consider co-administering the hepatitis A vaccine with the pentavalent vaccine (diphtheria-tetanus-pertussis (DTP), Haemophilus influenza type b (Hib) and hepatitis B), which was introduced in Indonesia in mid-2013 [55]. Although the prices of the combined vaccines are higher than the prices of the monovalent vaccines, the initial higher cost would be recouped in the future through its capabilities of generating savings on direct and indirect costs, as experienced during the introduction of the pentavalent vaccine in Indonesia [56]. Another approach is through intensifying research and development to produce affordable non-traditional vaccines locally. With respect to the rotavirus vaccine, the Indonesian government is already considering manufacturing a rotavirus vaccine in mass production through Biofarma, in collaboration with the Murdoch Children Research Institute (MCRI), in order to secure long-term sustainability of the vaccine supply [57]. Other strategies to improve efficiency are reducing vaccine wastage, strengthening procurement strategies and improving management and planning strategies, according to a review study [46].

The final recommendation is to improve preventive interventions. It should be underlined that the immunization program in Indonesia is only one component in a comprehensive approach to prevent and control diseases. In order to achieve a continuous reduction in mortality rate over the next few years, it is important to continue intensifying

efforts related to broader preventive interventions, such as promoting breastfeeding and improving sanitation. A study on estimating the effect of breastfeeding-promotion interventions on the cost-effectiveness of rotavirus immunization in Indonesia confirmed that breastfeeding promotion provides some potential to reduce the treatment costs for rotavirus immunization in Indonesia due to its effect on reducing rotavirus-diarrhea cases [10]. Furthermore, previous studies on the cost-effectiveness of hepatitis A in several countries reported that the incidence rate of HAV is strongly and conversely correlated with improvements in sanitation [58,59].

Interpreting the results from two studies on the cost-effectiveness of rotavirus immunization in Indonesia and one study on the economic evaluations of hepatitis A immunization in MICs, the implementation of non-traditional vaccines potentially could be cost-effective interventions in MICs, particularly in Indonesia [9,10,56]. Also, the most influential factors toward implementation of these vaccines were vaccine price, medical costs, number of incidences, vaccine efficacy and mortality rate [9,10,56]. As reported in many countries, vaccine price has been identified as one of the most important factors in influencing decisions to introduce a new vaccine [60]. However, a study by Milstein *et al.*, focusing exclusively in MICs, argued that vaccine price might not be the major driving factor in terms of affordability and in conjunction with other factors, such as perceived impact and policy context [61]. In the case of introducing the rotavirus vaccine, the price of rotavirus vaccines (US$ 5 per dose) is relatively high compared to the price of other, traditional vaccines, such as the DTP vaccine (US$ 0.14 per dose) [9,62,63]. To overcome this issue, the government needs to produce affordable rotavirus vaccines by itself as soon as possible within its own jurisdiction to secure the long-term sustainability of the vaccine supply when there is no external financial support for rotavirus immunization. Regarding the hepatitis A vaccine, the most realistic strategy to finance the universal hepatitis A immunization in Indonesia is through creating new fiscal space, which could be created from efficiency gains in other health interventions or other immunization programs [63]. Also, creating innovative mechanisms could be used for paying the incremental costs of both traditional and non-traditional vaccines in Indonesia, including the rotavirus and hepatitis A vaccines [63].

Expert commentary

Implementation of non-traditional vaccines into the EPI in Indonesia is still facing many challenges. Firstly, although the immunization budget accounts for only a small portion of the Indonesian government health budget, it has to share limited public health resources with many competing priorities, such as financing public hospitals, curative care services,

and other major public health programs (*e.g.,* HIV/AIDS treatment and prevention). Since the price of non-traditional vaccines, such as rotavirus and hepatitis A vaccines, is relatively expensive, it should be highlighted that implementation of these vaccines would stretch the immunization budget up to three or four times its present level [64]. Secondly, it is very important to ensure the sustainability of a new additional program so that it would be financed over the medium or long term, and it would not endanger the sustainability of the Indonesian government's financial position. Thirdly, as has occurred in several countries, donor support for immunization programs is often volatile and unpredictable. This characteristic interrupts the ability of countries with a limited health budget, such as Indonesia, to plan for the overall finance program and to anticipate future needs and funding gaps [46]. In particular, increasing reliability of funding would help the Indonesian government to strengthen immunization services. However, budgeting and financial analyses are important tools for policymakers to estimate the available budget for the EPI within limited resources, because it has been reported in many developing countries that failures in implementing new immunization programs were mostly caused by shortfalls in vaccine program funding.

Five-year view

As the impact of vaccines on public health has increased significantly in the last decade, funding for new vaccine development and introduction has surged. Countries all over the world, such as Indonesia, are now beginning to add non-traditional vaccines into their traditional immunization programs. However, the vaccine supply chain and logistics systems used in most of these countries were developed many years ago when vaccination cost was still extremely low, and before the wide use of sophisticated tracking and modern tools. To tackle this issue in the next five years, several improvements in the management of the vaccine supply chain should be urgently executed to accommodate the introduction of additional immunization programs. At the same time, other programs to increase efficiency of immunization programs (*e.g.,* avoiding stock-outs, minimizing wastage, and improving safe and efficient vaccine management) should be improved continuously because of the rising costs of vaccination.

Despite the growing number of non-traditional vaccines in the last few years, reliable data related to disease burden and economic evaluations of non-traditional immunizations in Indonesia are still poorly documented. This might lead to concerns because assessments of these vaccines as being too costly were often made by the research community without considering optional strategies. To help policy makers in Indonesia to make informed

choices about the best way to spend the limited resources available for healthcare, the research community must come up with more convincing and locally relevant evidence. Thus, further high-quality economic evaluations on the cost-effectiveness of non-traditional immunizations under different settings and from different perspectives are still required over the next five years.

Key issues

- We found that the introduction of non-traditional vaccines in Indonesia is still facing many challenges.
- There are four strategies to finance new vaccines that can be applied in Indonesia using the experience of other countries: governments fully finance the EPI and additional vaccines, donors only finance the additional vaccines, governments finance the additional vaccines, and governments charge user fees only for the additional vaccines.
- There are several innovative mechanisms to overcome financial barriers related to the immunization programs, such as levies on airline tickets, simple and hassle-free donation, public-private partnerships in action, and levies on automotive sales
- We recommended several strategies to strengthen the immunization programs in Indonesia, such as budgeting and financial reforms, decentralization reforms, improving the efficiency of immunization and preventive interventions.

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Summary

Since the Expanded Program on Immunization (EPI) was launched by the Ministry of Health in 1977, vaccinations have been the most important contributors to reduce childhood mortality and increase life expectancy in Indonesia. In addition to the use of traditional vaccines in the EPI, the Indonesian government still needs to introduce additional vaccines to further reduce rates of childhood mortality (Chapter 1). Despite the importance of health economic evaluations in assessing healthcare interventions, very few economic evaluation studies on non-traditional immunization have been conducted in Indonesia. Motivated by this, I and my co-authors propose a framework on economic evaluations of non-traditional vaccinations in Indonesia by using two reference cases of rotavirus and hepatitis A vaccines in the first and second part of this thesis, respectively.

In the first part of this thesis, the cost-effectiveness of rotavirus immunization in Indonesia was explored initially by taking breastfeeding patterns into account (Chapter 2). Applying a three-dose rotavirus vaccine (Rotateq®) and considering its market price at US$ 5 per dose, rotavirus immunization program in Indonesia could be a highly cost-effective intervention. In particular, a further research which took the effect of breastfeeding promotion into account (Chapter 3), confirmed that breastfeeding promotion provides some potentials to reduce the treatment costs for rotavirus immunization in Indonesia due to its effect on decreasing rotavirus-diarrhea cases. To give an idea of the situation in another MIC, in Chapter 4, the cost-effectiveness of rotavirus immunization in Hangzhou, China was analyzed by making a comparison between two vaccines (Rotateq® and LLR®). In the context of the health economic perspective, we concluded that the implementation of LLR® would be more realistic to be implemented in China than Rotateq®. Based on the summary of evidence supporting introduction of rotavirus vaccination in Indonesia, in Chapter 5, we discussed the constraints and draw upon experiences from other countries to propose strategies that would help to accelerate the introduction of rotavirus immunization in Indonesia. We found that delay in the introduction of new vaccines in middle-income countries, such as Indonesia, may be attributed to multiple factors, such as perceived vaccine value, health system characteristics and policy considerations.

In the second part of this thesis, a comprehensive picture of hepatitis A vaccination in MICs was presented in a systematic review (Chapter 6). We found that vaccine price, medical costs, incidence and discount rate were the most influential parameters on the sensitivity analyses. Vaccine price has been shown as a barrier for middle-income countries in

implementing universal vaccination of hepatitis A. Specifically, a cost-effectiveness analysis of hepatitis A immunization in Indonesia was presented in Chapter 7. We summarized that the implementation of hepatitis A immunization in Indonesia would be a cost-effective health intervention under the market vaccine prices. Given the budget limitations, the use of a one-dose vaccine schedule would be more realistic to be applied than a two-dose vaccine schedule.

In conclusion, the introduction of non-traditional vaccines in Indonesia is still facing many challenges (Chapter 8), with cost-effectiveness however not seeming to be a major obstacle. Given its relatively limited immunization budget, the implementation of non-traditional vaccines in Indonesia appears to be strongly dependent on the finance arrangement of the immunization programs. New sources of development financing are required to be pushed to ensure the sustainability of new additional programs.

Samenvatting

Sinds de introductie van de “Expanded Program on Immunization” (EPI) door de “Ministry of Health” van Indonesië in 1977, maken vaccinaties een belangrijk deel uit van alle initiatieven om kindersterfte te reduceren en de levensverwachting te verhogen. Naast het gebruik van traditionele vaccins binnen de EPI, moet de overhead echter nog steeds besluitvorming ontwikkelen omtrent de introductie van nieuwe vaccins om de gezondheid verder te bevorderen (Hoofdstuk 1). Ondanks het belang van gezondheidseconomische analyses bij nieuwe interventies in de zorg, zijn er in Indonesië maar zeer beperkt economische evaluaties beschikbaar van niet-traditionele vaccins. Daarom ontwikkelden wij een raamwerk voor economische evaluaties van dergelijke vaccins met rotavirus en hepatitis A vaccins als voorbeelden in respectievelijk het eerste en tweede deel van dit proefschrift.

In Hoofdstuk 2 wordt de kosten-effectiviteit geschat van rotavirus immunisatie in Indonesië waarbij expliciet rekening wordt gehouden met het toepassen van bortsvoeding bij jonge moeders gezien de wederzijdse beïnvloeding van rotavirus vaccinatie en borstvoeding. Uitgaande van een 3-doses rotavirus vaccin (Rotateq®) en een markprijs van US$ 5 per dosis, is rotavirus immunisatie in Indonesië zeer kostent-effectief. Verder onderzoek gaf aan dat verdere stimulering van borstvoeding de kosten en het voorkomen van rotavirus diarrhea verlagen waarbij vaccinatie nog steeds kosten-effectief blijft (Hoofdstuk 3). Om een idee te geven van hoe ons raamwerk op een andere “Middle Income Countries” (MIC) zou kunnen worden toegepast, analyseerde ik in Hoofdstuk 4 met mijn co-auteurs de kosten-effectiviteit van rotavirus immunisatie in een stedelijk gebied in China door specifiek 2 vaccins the vergelijken (Rotateq® and LLR®). We concludeerden dat vanuit gezondheidseconomisch perspectief in China, implementatie van LLR® meer realistisch is dan Rotateq®. Uitgaande van een analyse van de beschikbare “evidence” voor mogelijke succesvolle introductie van rotavirus vaccins in Indonesië, worden in Hoofdstuk 5 the beperkingen bedicussieerd en gaan we uit van de situaties in vergelijkbare landen om tot aanbevelingen te komen hoe implementatie van rotavirus immunisatie in Indonesië versneld kan worden. Uitstel van introductie in vergelijkbare MICs was vaak te relateren aan diverse factoren zoals onzekerheid over de waarde van vaccins, karakteristieken van het gezondheidszorgsysteem en politieke factoren.

In het tweede deel van het proefschrift wordt allereerst een volledig beeld gegeven van hepatitis A vaccinatie in MICs binnen een systematische review (Hoofdstuk 6). Het blijkt dat

met name vaccin prijs, medische kosten, incidentie en de disconteringsvoet cruciale parameters zijn binnen een gevoeligheidsanalyse. Evenals bij het rotavirus vaccine, blijkt de prijs vaak een obstakel voor introductie van vaccinatie in MICs. In het bijzonder toont een kosten-effectiviteitsanalyse in Hoofdstuk 7 aan dat hepatitis A immunisatie in Indonesië kosten-effectief kan zijn, zelffs onder de huidige marktprijs. Gegeven echter de budget restricties, is een 1-dosis vaccinatie schema realistischer dan een schema met 2 doses.

Concluderend valt op te merken dat de introductie van niet-traditionele vaccins in Indonesië nog steeds voor hindernissen staat (Hoofdstuk 8), zonder dat overigens kosten-effectiviteit deze in de weg staat. Gegeven het beperkte budget voor immunisatie is introductie sterk afhankelijk van mogelijkheden financiële afspraken te kunnen maken met de industrie, GAVI en overheden. Verdere bronnen voor financiering ijn daarmee nodig om bestendige programma's te kunnen verkrijgen voor deze nieuwe vaccins.

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List of publications

1. Suwantika AA, Tu HA, Postma MJ. Cost-effectiveness of rotavirus immunization in Indonesia: taking breastfeeding patterns into account. *Vaccine* 31(32), 3300-3307 (2013).
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Curriculum vitae

Auliya Abdurrohim Suwantika was born in Tegal, Indonesia, 31 years ago. After finishing his high school in Banjarnegara, he moved to Bandung to take his bachelor and master degrees. He received his bachelor degree in pharmacy from the University of Padjadjaran in 2004 and his master degree in business administration from the Institut Teknologi Bandung in 2007. Upon his graduation, he decided to be an entrepreneur to apply his knowledge both in pharmacy and business administration by running a 24-hour pharmacy. During that time, he was also a pharmacist in a district government hospital and a guest lecturer for entrepreneurship course in the University of Padjadjaran. In 2011, he decided to pursue his doctoral degree in the Netherlands and wrote a research proposal, which was granted by the Directorate General of Higher Education, Ministry of National Education, Republic of Indonesia. In December 2011, he officially started his PhD research in the Unit of PharmacoEpidemiology & PharmacoEconomics, Department of Pharmacy, University of Groningen, under the supervision of Prof. Dr. Maarten J. Postma and Dr. Keri Lestari. His project was about economic evaluations of non-traditional vaccinations in middle-income countries by using Indonesia as a reference case and focusing on rotavirus and hepatitis A. After less than three years, Auliya Abdurrohim Suwantika will obtain his PhD degree in June 2014. He will continue his career as a lecturer in the Department of Pharmacology and Clinical Pharmacy, Faculty of Pharmacy, University of Padjadjaran, Bandung, thereafter.

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